Brain-Behavior Relationships in Healthy Aging:

A Multimodal Approach

Thesis

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SUMMARY

Aging is a multifactorial process including physical, psychological and social changes. With the development of high-technology medicine life expectancy has increased tremendously, leading to a shift in focus in medicine and research from physical problems to cognitive alterations. Given an increase in the proportion of older adults in the population, age-related cognitive decline is now considered a major health issue in the current century. Therefore, facilitation of healthy aging emerges as a leading research priority. Next to cognitive alterations (e.g., processing speed, executive functions and memory) (Buckner, 2004; Salthouse, 1996, 2003, 2009), deficits in motor performance (e.g., slowing of movement, gait and balance difficulties and coordination of multi-joint movement; for a review: Seidler et al., 2010) are also apparent in older adults. Because age-related deteriorations in cognitive and motor abilities have far-reaching consequences such as decline in life satisfaction and quality of life (Abrahamson, Clark, Perkins, & Arling, 2012; St John & Montgomery, 2010), as well as difficulties in activities of daily living, identifying underlying mechanisms is crucial. However, the neuroanatomical and neurofunctional underpinnings of cognitive and motor behavior are still not precisely understood. Based on a multimodal analysis approach of magnetic resonance imaging (MRI) sequences, which is considered as a cutting-edge technique in neuroimaging research, the present thesis aims to gain further insight in the relationship between brain and behavior.

Both studies in this dissertation are based on a large, well-educated and healthy sample from the "Longitudinal Healthy Aging Brain" (LHAB) database project conducted at the International Normal Aging and Plasticity Imaging Center (INAPIC).

By the use of joint analysis of two MRI modalities, the first study aimed to gain more insight into the white matter tissue class of the brain. In addition to macrostructural measures, such as volumes for white matter hyperintensities (WMH) and normal appearing white matter

(NAWM; white matter in the cerebrum outside WMH), white matter microstructural integrity within WMH and NAWM was evaluated in this study. In a second step, white matter properties were related to several clearly defined measures of executive functioning and processing speed.

The results emphasize the importance to distinguish and analyze white matter integrity within and outside WMH separately since white matter integrity within WMH is not only significantly lower, but also differently associated with cognitive abilities than white matter integrity within NAWM.

The second study investigated the relationship between the structural and functional connectivity of the cingulum bundle, a white matter pathway connecting two major hubs of the default mode network, and their relationship with cognitive and motor performance within the context of healthy aging. The overarching aim of the study was to examine if functional connectivity explains unique variance, in addition to the amount explained by structural connectivity in cognitive and motor performance, using hierarchical regressions. The results show neither a relationship between structural and functional connectivity of the cingulum bundle nor an association between functional connectivity strength and age. Nonetheless, a relation between white matter integrity of the cingulum bundle and age is apparent. Further, functional connectivity strength is a predictor for individual differences in cognitive and motor behavior tests with a strong speed component, whereas no additive effect is found including structural and functional connectivity measures in the same hierarchical regression model. Nevertheless, the findings indicate that maintained functional connectivity strength may be of great importance for healthy cognitive aging despite white matter integrity loss.

ZUSAMMENFASSUNG

Altern ist ein von vielen verschiedenen Faktoren beeinflusster und interindividuell sehr unterschiedlich verlaufender Prozess, der auch von physischen, psychischen und kognitiven Veränderungen geprägt ist. Mit der stetig ansteigenden Lebenserwartung steigt auch der Anteil älterer Menschen und Hochbetagten an der Gesamtbevölkerung. Als Folge dieser demographischen Entwicklung ist der Unterschied zwischen gesundem versus pathologischem Altern vermehrt in den Fokus der Forschung gerückt. Nicht nur wird gerade das Nachlassen der kognitiven Fähigkeiten im Alter von den Betroffenen als besonders einschneidend für deren Lebensqualität und –zufriedenheit erlebt, sondern stellt auch die Gesamtgesellschaft vor grosse Herausforderungen im Gesundheitsbereich und steht darum besonders im Zentrum der Aufmerksamkeit der Forschung. Somit ist die Erforschung der zugrundeliegenden Mechanismen der kognitiven Beeinträchtigung von grösster Wichtigkeit. Über die Zusammenhänge zwischen dem Ausmass des kognitiven Abbaus und den Veränderungen der Gehirnanatomie im Kontext gesunden Alterns ist jedoch wenig bekannt.

Das Ziel dieser Dissertation besteht darin, durch die Kombination verschiedener magnetresonanztomographischer (MRT) Aufnahmen der Komplexität des Gehirns besser Rechnung tragen zu können und damit einen tieferen Einblick in den Zusammenhang zwischen Verhalten und Gehirn zu erhalten. Beide Studien im Rahmen dieser Dissertation basieren auf Daten des ersten Messzeitpunktes des Longitudinal Healthy Aging Brain (LHAB) Datenbank-Projektes, welches am Kompetenzzentrum für Plastizität im Alter an der Universität Zürich durchgeführt wird. Die in dieser Datenbank erfasste, zahlenmässig grosse Stichprobe zeichnet sich durch eine überdurchschnittlich gute Bildung und Gesundheit für ihre Altersklasse aus.

Das Ziel der ersten Studie war es, die Integrität der normal erscheinenden weissen Substanz und der krankhaft veränderten weissen Substanz, welche auch als Läsion bezeichnet wird und

im MRT-Signal heller bzw. hyperintens erscheint, detaillierter zu erforschen und den Zusammenhang zwischen diesen Charakteristika und psychometrischen kognitiven Tests (Exekutivfunktionen und Wahrnehmungsgeschwindigkeit) zu untersuchen. Dabei wurde die Integrität der weissen Substanz im normal erscheinenden sowie hyperintensem Gewebe quantifiziert und zu den erzielten Leistungen in den kognitiven Tests in Bezug gesetzt. Die Resultate zeigen, dass Integritätswerte der weissen Substanz innerhalb der Läsionen signifikant tiefer sind als in der normal erscheinenden weissen Substanz. Weiter waren die Integritätswerte innerhalb und ausserhalb der Läsionen unterschiedlich mit den kognitiven Leistungen assoziiert. Beide Resultate weisen darauf hin, dass es nicht ausreicht, nur das Volumen der weissen Substanz zu untersuchen. Eher sollte die weisse Substanz zuerst bezüglich ihrer Integrität klassifiziert werden. Weiter zeigen unsere Resultate, dass der Grad der Intaktheit in den Läsionen positiv mit Verhaltensdaten korreliert, wohingegen kein Zusammenhang zwischen der Grösse der Läsion und der kognitiven Leistungsfähigkeit gefunden wurde. Diese Ergebnisse legen die Schlussfolgerung nahe, dass weniger die Grösse der Läsion, sondern eher der Grad der Beschädigung einen Prädiktor für den Erhalt der Leistungsfähigkeit im Alter darstellt.

Die zweite Studie untersuchte die Beschaffenheit der strukturellen und funktionellen Verbindungen zwischen zwei spezifischen Hirnarealen des „Default Mode Networks“ und beabsichtigte die strukturellen und funktionellen Marker mit kognitiven und motorischen Fähigkeiten in Verbindung zu bringen. Weiter wurde untersucht, ob die Kombination der strukturellen und funktionellen Daten mehr Varianz hinsichtlich des beobachteten Verhaltens aufklärt als beide Marker getrennt. Die Datenanalyse zeigte jedoch keine additiven Effekte, d.h. die Kombination struktureller und funktioneller Verbindungsparameter trägt in unserem Datensatz nicht zu einer grösseren Varianzerklärung kognitiver und motorischer Fähigkeiten bei. Die Stärke der funktionellen Verbindung zwischen den beiden Arealen scheint jedoch ein

Prädiktor für die kognitive Leistungsfähigkeit zu sein, insbesondere für diejenigen Fähigkeiten, die stark durch die Wahrnehmungsgeschwindigkeit beeinflusst sind. Da nur strukturelle Verbindungen einen Zusammenhang mit dem Alter aufwiesen, darf angenommen werden, dass die Aufrechterhaltung funktioneller Verbindungen trotz der Beeinträchtigung struktureller Integrität möglich ist und für das gesunde Altern von grosser Wichtigkeit zu sein scheint.

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LIST OF ABBREVIATIONS

AD	Axial Diffusivity
BOLD	Blood Oxygenated Level-Dependent
CC	Corpus Callosum
CSF	Cerebrospinal Fluid
DTI	Diffusion Tensor Imaging
DMN	Default Mode Network
DPARSF	Data Processing Assistant for Resting-State fMRI
EEG	Electroencephalography
EF	Executive Functions
FA	Fractional Anisotropy
FLAIR	Fluid Attenuated Inversion Recovery
fMRI	functional Magnetic Resonance Imaging
FSL	FMRIB's Software Library
GLM	General Linear Model
ICA	Independent Component Analysis
ICV	Intracranial Volume
IP	Inhibition Performance
INAPIC	International Normal Aging and Plasticity Imaging Center
LHAB	Longitudinal Healthy Aging Brain
MD	Mean Diffusivity
MMSE	Mini-Mental State Exam
mPFC	medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NAWM	Normal Appearing White Matter

PCC	Posterior Cingulate Cortex
PET	Positron Emission Topography
PS	Processing Speed
REST	Resting-State fMRI Data Analysis Toolkit
rs-fMRI	resting-state functional Magnetic Resonance Imaging
RT	Reaction Time
RD	Radial Diffusivity
ROI	Region Of Interest
SD	Standard Deviation
SPSS	Statistical Package for Social Science
TBSS	Tract-Based Spatial Statistics
TMT	Trail Making Test
TP	Time Point
WMH	White Matter Hyperintensities

1 INTRODUCTION

The aging process can be described as multifactorial, accompanied by physical, cognitive and social changes. With life expectancy increasing constantly, Switzerland is facing a demographic shift in the near future. As there are strong ties between aging and changes or decline in cognitive abilities, cognitive frailty is emerging as one of the most highly discussed health topics of the current century. These cognitive alterations, which are an undeniable part of the aging process, are evident in different domains. For example, processing speed, executive functions, as well as episodic memory, are especially affected (Buckner, 2004; Eckert, 2011; Head, Kennedy, Rodrigue, & Raz, 2009; Salthouse, 1996). Significant alterations in motor performance are also apparent with increasing age, predominantly in areas such as slowing of movement, gait and balance difficulties and coordination of multi-joint movement (Seidler et al., 2010). Because age-related decline in cognition and motor performance has far-reaching consequences such as reduction in life satisfaction and quality of life (Abrahamson et al., 2012; St John & Montgomery, 2010), as well as difficulties in activities of daily living, identifying underlying mechanisms is crucial. Such behavioral changes are likely related to alterations in brain structures and functions. Consequently, gaining insight into the aging brain has become a research priority over the last years. During the last two decades, cortical gray matter characterized by its thickness, surface area or volume was predominantly used to analyze the brain-behavior relationship. With the development of diffusion tensor imaging (DTI), the exploration of white matter became more emphasized. Instead of examining separate cortical brain regions, DTI takes cortical connections via white matter fiber tracts into consideration, and underlines the importance of these connections among brain areas (Sullivan & Pfefferbaum, 2006). This long-neglected white matter network gains more and more importance, since defects of the “wiring” likely

have widespread impact on communication between cortical regions, and consequently influence behavioral functions. Furthermore, to account for the complexity of the human brain, the combination of several magnetic resonance imaging (MRI) sequences (multimodal imaging) increased in popularity.

Studies investigating the underlying mechanisms of the decline in cognitive and motor performance in the context of healthy aging are crucial for several reasons. First, more information about structural changes offers the possibility of explaining behavioral changes; second, better knowledge about healthy aging helps us to understand and to evaluate strategies, which enable individuals to maintain cognitive and motor function in old age.

By means of joint analysis of different MRI sequences, the overall aim of the present thesis is to gain a more elaborated picture about the aging brain and thus gain additional insight into the brain-behavioral relationship.

In the first part of chapter two, an outline of previous findings on behavioral differences and neurostructural and -functional alterations in healthy aging is presented. In the second part of chapter two, the concept of "cortical disconnection" and its impact on cognition and functional connectivity is described. An overview about multimodal imaging, which could help attain deeper knowledge about the disconnection of the aging brain, is reviewed in part three of chapter two. In chapter three, two main research questions are specified. Additionally, principles for different MRI sequences used in this thesis are delineated in chapter four. In chapter five, two empirical studies are presented, which address the stated research questions in chapter three. Finally, chapter six comprises of an overall discussion of the two studies and provides suggestions for future research.

2 THEORETICAL BACKGROUND

2.1 NEUROANATOMICAL AND COGNITIVE DIFFERENCES IN HEALTHY AGING

2.1.1 COGNITIVE AND MOTOR PERFORMANCE

Differences in cognitive functions with increasing age are well studied; difficulties emerge in abilities such as reasoning, executive functions, and processing speed (Grady, 2012; Salthouse, 2004). These skills fall under the term fluid intelligence, one of the two components within the framework of the concept of fluid and crystallized intelligence (Cattell, 1963). In contrast to fluid intelligence, performance in tasks of crystallized intelligence (e.g., vocabulary, general knowledge) remains stable or even increases over the life course (J. L. Horn & Cattell, 1967). To illustrate, results from Park and colleagues (Park et al., 2002) indicate that performance in tests measuring fluid intelligence declined with increasing age. Contrary, verbal knowledge was positively affected by age (Figure 1).

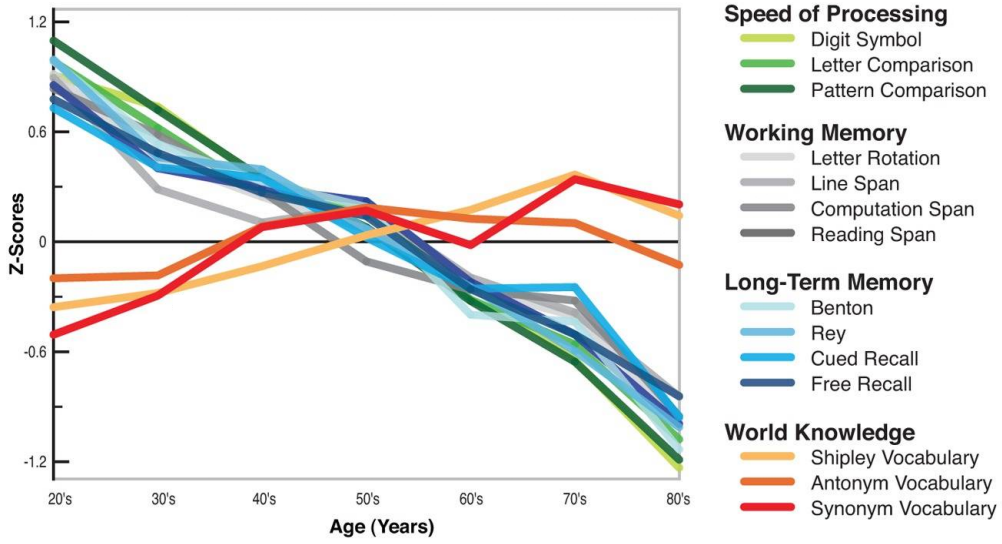

Figure 1. Cross-sectional data showing the differences between behavioral performance in distinct cognitive domains (speed of processing, working memory, long-term memory and verbal knowledge)
Simplified version adapted from (Park & Reuter-Lorenz, 2009)

To understand the causes of age-related alterations in cognitive abilities, several theories of cognitive aging have been proposed. Two of the most influential models are the *processing speed* theory (Salthouse, 1996) and the *prefrontal-executive* theory (West, 1996). In the following section, a short overview of the two concepts is presented and the main cognitive abilities of both theories, processing speed (PS) and executive functions (EF), are described in more detail.

The *processing speed* theory proposes that general age-related slowing is the underlying mechanism for deterioration in other cognitive domains, such as memory or working memory (Verhaeghen & Salthouse, 1997). PS is defined as the speed at which the brain processes information. It is a measurement of mental efficiency and determines how fast one can execute mental operations (Salthouse, 2000). PS is further considered a central construct, which is particularly vulnerable to age-related decline and is related to global deterioration of white matter microstructural integrity throughout the brain (Eckert, Keren, Roberts, Calhoun, & Harris, 2010; Salthouse, 1996).

In contrast, the *prefrontal-executive* theory postulates that age-related deterioration of the frontal lobe is specifically associated with executive function performance. Therefore, this theory emphasizes a more local structural deterioration in the brain. EF are defined as top-down control processes, which plan, coordinate and monitor other cognitive processes and enable, through their regulatory mechanisms, goal-directed and situation-specific behavior (O'Sullivan, Barrick, Morris, Clark, & Markus, 2005; Salthouse, Atkinson, & Berish, 2003). Thus, within the framework of this theory, decline in EF is seen as the predictor for general cognitive deficits.

Although EF are a common research target, they are only vaguely defined, due to their complexity. A theoretical classification of EF, which is widely used, was proposed by Miyake and colleagues (Miyake et al., 2000). In this model, three related yet distinct subcomponents

of EF are introduced: updating, task-switching and inhibition. Based on the absence of a clear definition of EF, neuropsychological tests used to assess EF differ substantially, and actual distinguishable subcomponents are commonly combined in EF composite scores. Moreover, the *processing speed* theory and the *prefrontal-executive* theory are shown to share mutual variance.

Thus, controlling for general processing speed is crucial when investigating EF measures. In the present thesis commonly used scores, which should adequately control for PS, are compared to gain further insight about the validity of EF measures.

Besides cognitive alterations, decreases in sensorimotor control and functioning are prevalent with increasing age, leading to difficulties with gait and balance (Tang & Woollacott, 1996) but also to slowing of movements (Diggles-Buckles, 1993). In this thesis, focus was laid on fine motor skills rather than gross sensory motor skills (e.g., balance), since precise control over the upper extremities, including hands and fingers, is crucial for most activities of daily living and maintenance of independence in old age.

2.1.2 White Matter Macro- and Microstructure

Along with behavioral changes, brain alterations are found with increasing age. In general, macrostructural white matter changes such as white matter volume decline and abnormal white matter MRI signal increases are reported in the aging process (Brickman et al., 2011; de Groot, Oudkerk, Gijn, & Hofman, 2000; Guttmann et al., 1998).

Abnormal white matter MRI signals are described as white matter hyperintensities (WMH) or as leukoaraiosis/leukoencephalopathy. They were originally referred to as “unidentifiable, bright objects” which were considered as measurement artifacts (Brickman, Muraskin, & Zimmerman, 2009). Although WMH are more prevalent in mild cognitive impaired or participants with Alzheimer’s Disease, WMH burden also increases in older people without any sign of cognitive impairment (de Groot et al., 2000; Yoshita et al., 2006). The age-related

increase in WMH is reported to be not uniform over the brain since the frontal lobe seems to be more affected than more posterior parts. Additionally, WMH can be categorized by location. WMH flanking the ventricles are described as periventricular, whereas hyperintensities in the subcortical area are depicted as deep white matter lesions (Brickman et al., 2009; O'Brien et al., 2002). It is assumed that periventricular WMH not only appear earlier than deep white matter lesions but also increase in volume faster (Silbert, Howieson, Dodge, & Kaye, 2009; Silbert, Nelson, Howieson, & Moore, 2008). Besides age, which seems to be the most robust predictor for WMH, several risk factors are known for WMH progression (e.g., male sex, hypertension, high systolic blood pressure, previous stroke, body mass index, high-density lipoprotein, and triglyceride levels) (Gouw et al., 2008). Although the underlying pathology is still not clearly understood, it is hypothesized that WMH are mainly caused by myelin degeneration and small vessel loss (Murray et al., 2012).

With the emergence of diffusion tensor imaging (DTI), not only macrostructural changes but also white matter microstructural integrity could be analyzed (Madden et al., 2012). There is clear evidence for declining white matter integrity with advancing age in the context of healthy aging (Barrick, Charlton, Clark, & Markus, 2010; Burzynska et al., 2010; Madden, Bennett, & Song, 2009; Sullivan & Pfefferbaum, 2006). Several reasons were proposed to be responsible for the integrity change, such as deterioration of myelin sheaths, which causes increased diffusion perpendicular to fiber tracts (Peters, 2002). Furthermore, axonal degeneration resulting in decreasing axonal density also leads to higher diffusion, since larger extracellular space between axons exists (Sullivan & Pfefferbaum, 2006). Studies applying DTI in general find that fractional anisotropy (FA) decreases and mean diffusivity (MD) increases with advanced age, with differences more pronounced for anterior than for posterior regions of the brain (Charlton, Schiavone, Barrick, Morris, & Markus, 2009; Madden et al., 2009; Sullivan & Pfefferbaum, 2006). In addition, radial diffusivity (RD) is robustly reported

to increase with age, whereas both age-related increases and decreases in axial diffusivity (AD) have been found (Bennett & Madden, 2014).

Although the relationship between age and white matter integrity is not yet fully understood, white matter fiber tracts are obviously prone to damage in aging.

2.1.3 RESTING-STATE FUNCTIONAL CONNECTIVITY

Resting-state functional connectivity has been used to investigate age-related differences in a variety of brain networks. Out of these, the default mode network (DMN) is one that has been most studied with respect to aging because regions contained in the network are highly linked to Alzheimer's disease (e.g., hippocampus) (Buckner, 2005). In general, studies investigating functional connectivity strength between regions of the DMN found a negative relationship with age (Dennis & Thompson, 2014; Ferreira & Busatto, 2013). However, the studies reviewed by Dennis and Thompson (2014) based their assumption about decreased functional connectivity strength in healthy aging on results comparing relatively small groups of younger versus older participants. It could be argued that those studies are only comparing extreme groups and that they possibly miss subtle differences, which may be apparent among older people. However, cross-sectional analysis over a larger age-range (e.g., 19 to 80 years of age) support findings from group comparisons as they found a linear decline of functional connectivity strength over the life span (Mevel et al., 2013; Onoda, Ishihara, & Yamaguchi, 2012). Additionally, studies investigating the relationship between age and functional connectivity strength within a sample of older participants depict also a significant decrease in connectivity with increasing age (Andrews-Hanna et al., 2007). In contrast, a recent longitudinal study by Persson and coauthors (2014) investigating participants with a mean age of 65.2 (range 49-79 years) at the first measurement time point, found no change in DMN connectivity strength within a test-retest period of 6 years. Thus, additional longitudinal studies are needed to gain more profound knowledge about the functional connectivity

changes associated with healthy aging, as mixed results between cross-sectional and longitudinal analyses are apparent.

One possible cause for the weakening in functional connectivity strength could be explained by the cortical disconnection hypothesis as decline in underlying white matter tracts may influence functional connectivity strength. To explore this assumption joint analysis of multiple MRI sequences are needed.

Both, the cortical disconnection hypotheses and the combined analysis of several MR images are described in the next parts of this dissertation.

2.2 DISCONNECTION HYPOTHESIS

White matter can also be described as the fiber tracts, which unite different brain regions into networks. This means that damage or age-related decline in white matter integrity could lead to disturbance in brain functioning. The importance of white matter networks for higher order cognitive functioning was first described by Geschwind in 1965 (Geschwind, 1965). The concept of "cortical disconnection" as an underlying cause of behavioral deterioration and functional connectivity loss was then proposed by O'Sullivan and colleagues (2001). This concept is supported by findings, which show that age-related differences in white matter integrity are linked to cognitive functions, such as executive functions, working memory and processing speed (Bai et al., 2011; Bennett & Madden, 2014; Charlton et al., 2006; Kennedy & Raz, 2009). WMH could also have an impact on the fiber network since they might cause disruption of fiber tracts. Associations between WMH and cognitive decline are also reported but with slightly mixed results (for a review: Mortamais, Artero, & Ritchie, 2013). It could be argued that WMH are therefore less specific than DTI estimates to assess white matter tract deterioration that leads to cortical disconnection.

Since white matter tracts depict the neuroanatomical structure for functional connectivity between brain regions, the loss in functional connectivity strength can also be explained by

the cortical disconnection hypothesis. Studies combining different MR images to analyze association between structural and functional connectivity are still scant in the field of healthy aging (see chapter 2.3 for detailed information). However, a better knowledge about the structure-function relationship is needed since not only white matter integrity but also functional connectivity strength has been associated with behavior measures. To illustrate, within the DMN functional connectivity strength was found to be positively related to cognitive performance like memory retrieval, executive functions and processing speed (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Ferreira & Busatto, 2013; He, Carmichael, et al., 2012; Mevel et al., 2013). Moreover, next to the DMN, several previous studies, including a study from our laboratory, have found that functional connectivity strength within the sensorimotor network is associated with motor performance (Fling & Seidler, 2012; Langan et al., 2010; Seidler, Hirsiger, et al., 2014).

Since white matter and functional connectivity are related to behavioral measures, the question arises if white matter as an underlying structure could mediate the relationship between functional connectivity strength and cognition. To answer this question, joint analyses of multiple MR sequences combined with behavioral measures need to be conducted. The next section gives a short overview on multimodal imaging and a summary about previous work in this field.

2.3 MULTIMODAL IMAGING

It is obvious that one MRI sequence cannot rudimentarily capture the intricacy of the human brain alone. Thus, multimodal neuroimaging combines different MRI sequences, with the aim to increase the understanding of the brain by utilizing complementary information from distinct MRI images. Multimodal imaging is not restricted to the combination of multiple MRI sequences but also refers to the combination of different neuroimaging techniques such as positron emission topography (PET) as well as electroencephalography (EEG) and many

more. Further, each modality as well as MRI sequence is optimized for a specific aim and therefore has its own limitations, which a multimodal analysis intends to overcome. Thus, multimodal imaging combines different modalities in such a manner, that an added benefit is apparent compared to results from single modalities.

In this dissertation we restricted our analyses to co-investigate different MR images within the same study. To date, the most common approach for multimodal MR data integration is the combined analyses of DTI and resting-state functional MRI recordings to gain more insight into the relationship between the structural and functional connectivity of the brain. Studies investigating this relationship generally report that healthy younger participants' structural connectivity is positively associated with functional connectivity strength (Damoiseaux & Greicius, 2009). When investigating patients, findings revealed that Alzheimer's disease might be related to decreased associations between structural and functional connectivity (Sun et al., 2014). Despite the interesting findings, studies analyzing the association between structural and functional connectivity are relatively rare in the field of healthy aging but in general show results similar to studies investigating younger participants. To illustrate, one study found that integrity of the white matter tract connecting the posterior cingulate cortex (PCC) and hippocampus was associated with functional connectivity strength between the two regions (Teipel et al., 2010). Additionally, functional connectivity strength between the PCC and the medial prefrontal cortex (mPFC) was related to white matter integrity in a larger region of interest (ROI) containing the cingulum bundle (Andrews-Hanna et al., 2007). It is therefore argued that integrity of structural connectivity is important for functional connectivity strength. However, there are also functional connections found between regions without a direct anatomical linkage (Honey et al., 2009; Sun et al., 2014).

Joint MR sequence analyses can also integrate images of the same tissue class. For example, additional information can be gained about the consistency of WMH by combining different

white matter recordings (DTI and WMH data). There are only a few studies that reported diffusion metrics separately for white matter outside and inside the WMH (Jokinen et al., 2013; Schmidt et al., 2010; Vernooij et al., 2009). The combined analyses with cognitive data revealed that the relationship between cognitive abilities was different for microstructural integrity outside and within WMH in the general population and in people with mild to severe WMH burdens. Since it is suggested that white matter degeneration progresses continuously with WMH depicting the most advanced stage (Maillard et al., 2013), analyzing white matter integrity in less affected participants could be of great value to gain insight into the course of WMH development.

Therefore, in the first study, MR images from the same tissue class (white matter) are combined to clarify the differences between white matter integrity inside and outside WMH in healthy aged participants. In the second study, DTI estimates and functional connectivity of two major hubs from the DMN are analyzed.

Combining a multimodal analysis with behavioral data could further improve the understanding of the brain-behavior relationship. So far, combining the analysis of more than one MRI modality, and cognitive/motor performance, has rarely been conducted in the context of healthy aging. Consequently, the next chapter describes two open research questions to fill this gap in the literature.

3 AIMS AND RESEARCH QUESTIONS

By relating behavioral outcome measures with a joint analysis of MR images, which potentially reveals orthogonal information about the aging brain, the overall aim of this dissertation was to gain further insight into the brain-behavior relationship. The importance of this endeavor is highlighted by the far-reaching impact of the intactness of cognitive and motor behavior on life satisfaction and quality of life. Although there is a growing body on literature of studies investigating the brain-behavior relationship, some questions still remain.

This dissertation aims to attain deeper knowledge about the brain-behavior relationship by answering two open research questions. In the next section, the questions accompanied by short study outlines are presented.

The first question relates to *white matter microstructural integrity within and outside white matter hyperintensities and its differential associations with clearly defined measures of executive functions and processing speed.* With increasing age, white matter microstructural integrity deterioration is apparent besides macrostructural changes, such as the increment in white matter hyperintensities (WMH). There is some evidence that white matter microstructural integrity is different within and outside WMH (e.g., Vernooij et al., 2009); however, it is not clear if this is true in healthy normal aging. Also unclear is how white matter integrity within and outside WMH relates to cognitive functioning. Study 1 addresses this question by a joint analysis of a diffusion tensor imaging and a fluid attenuated inversion recovery (FLAIR) MR sequence. Based on this analysis, WMH can be clearly distinguished from normal appearing white matter (NAWM), defined as the cerebral white matter that does not appear as hyperintense on a FLAIR image. For the analyses, microstructural integrity will be measured in both WMH and NAWM. Additionally, measures of two EF-subcomponents (i.e., inhibition and task-switching) and two PS scores will be collected to explore

associations between cognition and white matter integrity. Data will be analyzed with different general linear models.

The second question explores *if the combination of structural and functional connectivity serves as a better predictor for behavioral measures than each measurement separately.* Age-related behavioral declines might be the result of deterioration of white matter tracts, affecting brain structural and functional connectivity. To date, it is not clear if the combination of structural and functional connectivity data could better predict cognitive/motor performance than each measure alone. Study 2 has the goal to probe these relationships in the cingulum bundle, a major white matter pathway of the default mode functional network. By integrating the information from a DTI-based tractography and a resting-state functional MRI sequence, new information about associations between structural and functional connectivity will be gained. To broaden our knowledge about the brain-behavior relationship with the use of hierarchical regression models, neuroanatomical and functional data, both separately and combined, will be associated with measures of cognitive and motor functions.

4 METHODS

The present dissertation is conducted as part of the "Longitudinal Healthy Aging Brain" (LHAB) database project at the International Normal Aging and Plasticity Imaging Centre (INAPIC) in Zurich, Switzerland (Zöllig et al., 2011). Data acquisition started in July 2011 and the project is designed to span a time period of 5 years with annual cycles of data collection. The rationale of the LHAB database project is to investigate neuroanatomical and functional characteristics related to cognitive and motor performance scores. In addition, data was collected using multiple questionnaires about lifestyle, health and personality in order to identify factors that influence the course of healthy aging. Results will be compiled in a database that will serve as a rich resource for future research on healthy aging.

The next subsections outline the experimental design of the LHAB project, exclusion and inclusion criteria for participants and describe MRI sequences and analyzing methods used in this dissertation. Furthermore, the challenges emerging with big data sets are described.

4.1 SAMPLE

In the field of healthy aging research, sample characteristics are of major interest since distinctions in several aspects may yield variable outcomes. Such sample heterogeneity could consist of several factors. For one, samples may differ in size, which affects power with which results are detected. Analyzing a similar research question, the number of participants included in the project can vary from N~50 to N~900 (Kennedy & Raz, 2009; Vernooij et al., 2009). In addition, samples can differ considerably in age-range, which may lead to more variability within the data. Furthermore, cut-off scores for tests, which screen for cognitive impairment, may differ considerably, which is especially crucial when examining healthy aging. Including participants with Mini-Mental State Examination (MMSE; M. F. Folstein,

Folstein, & McHugh, 1975) scores as low as 24 clearly results in samples with different baseline cognitive abilities. Therefore, the LHAB project is characterized by strict exclusion criteria such as MMSE>26 (max. score 30) and self-reported history of neurological/psychiatric disease or diseases of the hematopoietic system (e.g., Anemia, Leukemia). In addition, participants are excluded if they suffered a traumatic brain injury less than two years ago or have been diagnosed with diabetes. Included were participants older than 64, German/Swiss German native speaker, right-handed and without contraindications for MRI. All participants who were initially recruited for the first time point were included in the analyses of this dissertation if they had complete MR data required for a specific research question and no missing measures for education and blood pressure.

4.2 EXPERIMENTAL DESIGN

The LHAB started in 2011 and relies on a longitudinal study design with five measurement time points (TP) (Figure 2). Once a year, the same group of participants is invited for data collection. In general, each TP consists of three sessions. Participants complete a psychometric test battery, which captures cognitive and motor functioning. Tests are administered at the INAPIC and last for approximately four hours. Next to a lunch-break, additional pauses were administered when needed. Secondly, participants undergo structural and functional MRI with a duration of one hour. Behavioral and MRI assessments are completed on different days within the same week. Thirdly, participants are asked to fill out surveys at home (online or in letter-form) on several topics covering health, medication, sleep, depression, memory, nutrition and leisure time activities. At TP 1, an additional mock scanner session has been offered to participants not familiar with the MRI application in order to accustom themselves to the MR scanner situation (particularly enclosed space and noise).

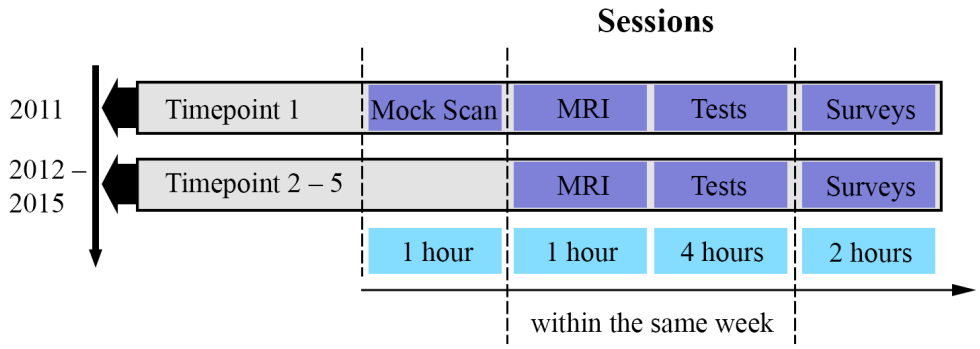

Figure 2. LHAB study design

4.3 MRI Analysis Methods

One of the major aims of this dissertation was to investigate the aging brain in a multimodal way. For this purpose, several MR sequences need to be collected within the same scan session, which applies for the LHAB database project.

In the next section fundamental principles for neuroanatomical (i.e., white matter characteristics) and functional images are described. In addition, different methods for analyzing the acquired sequences are briefly reviewed.

4.3.1 Structural Analysis

4.3.1.1 White Matter Hyperintensities

White matter hyperintensities (WMH) are abnormalities visible on T2-weighted MRI sequences, used to investigate white matter properties. The most commonly applied sequence to detect WMH is called FLAIR (Fluid Attenuated Inversion Recovery), which differs from normal T2-weighted images by suppressing the signal from the cerebrospinal fluid (CSF). This is important since CSF shows the same signal intensity as the WMH, which is especially problematic for periventricular WMH flanking the CSF filled ventricles. To achieve the signal suppression, a normal Spin-Echo-Sequence with a 180°-inversion pulse is applied. A relatively long inversion time allows the longitudinal magnetization of the CSF to return to

the null point before signal collection starts. Thus, CSF signal is fully suppressed in the image and WMH signals around the ventricles become emphasized compared to normal T2-weighted images (Brant-Zawadzki, Atkinson, Detrick, Bradley, & Scidmore, 1996). WMH depict longer T2 relaxation times compared to normal appearing white matter due to increased unbound water, which leads to higher signal intensity in the acquired image (Murray et al., 2012).

Several methods are used to analyze WMH. Within clinical settings, the predominating techniques are visual rating scales, such as the Scheltens and Fazekas scales (Fazekas, Chawluk, Alavi, Hurtig, & Zimmerman, 1987; Scheltens et al., 1993), which quantify the amount of WMH. Both scales account separately for periventricular or deep white matter lesions and grades are then given depending on number and size of lesions. Although visual rating scales are widely considered as the "gold standard", automatic procedures have become popular since WMH volumes can be quantified and parametric statistics test can be applied. However, operator-driven quantitative approaches still require user-based interventions. For example, intensity thresholds to specify voxels within WMH have to be defined and boundaries between WMH and CSF or brain tissue still need to be manually adjusted. In contrast, fully automated quantitative analytic processing streams are used to quantify WMH volume automatically with scant intervention by the researcher. The procedure consists of an iterative process whereby voxels are labeled if they fall in a determined intensity range for WMH (Brickman et al., 2011). Because we have been investigating a large sample of over 200 participants, the fully automatic procedure was chosen for analysis. In contrast to operator driven approaches, which utilize freely available software, fully automated approaches rely on in-house created analysis pipelines. Our WMH analysis was conducted in the Laboratory at the Columbia University in New York, headed by Professor Adam Brickman. Essentially, a voxel intensity histogram of each individual FLAIR image was

compiled. After fitting Gaussian curves to these distributions, the mean and standard deviation of the intensities were derived. In this study sample, WMH were defined as those voxels with an intensity higher than 1.7 x standard deviation above the mean.

4.3.1.2 WHITE MATTER INTEGRITY

Diffusion tensor imaging (DTI) offers a tool to investigate axonal organization of the brain and microstructural integrity of those fibers (Mori & Zhang, 2006). Since white matter integrity cannot be explored directly, DTI analysis rests upon diffusion of water molecules, which differs within distinct tissue types in the brain. To illustrate, within gray matter, as well as cerebrospinal fluids, diffusion is nearly non-directed since only few barriers (e.g., cell bodies for gray matter) or none (e.g., cerebrospinal fluids) are apparent. Such non-directed diffusion is normally described as isotropic. In contrast, diffusion in white matter is highly restricted by axonal cell membranes and myelin sheets, which leads to a facilitated diffusion along the fibers rather than a perpendicular diffusion. Thus, diffusion of water molecules within the white matter can be described as more directed (i.e., anisotropic) than in other brain tissues. (Bennett & Madden, 2014; Madden et al., 2012). After preprocessing the diffusion weighted images, the rate and directionality of water diffusion is represented in a 3D ellipsoid within each voxel. An ellipsoid can be described by its orientation of the axes (called eigenvectors) and length of the axes (called eigenvalues). Axial diffusivity (AD) represents the first eigenvector and describes diffusion parallel to the fiber tract, thus represent the fiber orientation. The average of the second and third eigenvectors is called radial diffusivity (RD) and describes diffusion perpendicular to the main direction of diffusion. The mean of all three eigenvalues represents the mean diffusivity (MD), which describes diffusivity within a voxel, regardless of directionality. However, the most frequently used measurement of white matter integrity using DTI is fractional anisotropy (FA) and represents the rate of orientation preference independent of the rate of diffusion within a tissue. FA values range from 0 to 1

with higher value indicating strongly restricted diffusion (Mori & Zhang, 2006). The DTI pre-processing result can be described as 3D tensor field, within which each tensor describes the dominant orientation of the voxel.

Various methods for analyzing DTI parameters have been suggested so far. Today, the most frequently used methods are tract-based spatial statistics (TBSS) or tractography (Madden et al., 2012). In TBSS analysis, diffusion weighted images from each participant are registered to a template and are then used to derive a so-called white matter skeleton. This skeleton represents the centers of fiber tracts, which are shared by the whole sample. In a next step, individual diffusion parameters of each participant are projected onto the skeleton. In contrast, tractography methods trace tracts based on seed regions of interest (ROI) (specific voxels(s)), for each participant separately. In general, by considering directionality information within each voxel, a continuous tracking line is conducted, which is stopped if it reaches a certain criteria for termination. Such criteria (depending on the method used) are indicated a priori and include thresholds for low anisotropy within a voxel to ensure that only white matter is traced or angle changes which inhibit "unnaturally" sharp turns during line propagation (Mori & van Zijl, 2002). Tractographies are classified into two methods based on different algorithms: deterministic and probabilistic. In deterministic tractography a single path is determined outgoing from a seed point by moving to a direction which is parallel to the main axis of the underlying diffusion tensor. Probabilistic tractography propagates not only one but several paths per seed point. After the tracking, the percentage of paths which have crossed a particular voxel is derived; by applying a threshold, more possible tracts will be retained (D. K. Jones, 2008).

In this dissertation, tractography was the preferred method over TBSS because the aim of the study was to track a fiber bundle between two defined ROIs. In addition, tracts may show substantial inter-individual differences especially in an aging population. Therefore, tracing

tracts for each participant separately is in our view the more appropriate method than projecting individual data on a whole sample based skeleton. Of the two tractography approaches, both have advantages and disadvantages, which have to be considered. To illustrate, because uncertainty increases with the length of the traceable path by using a probabilistic approach, deterministic tractography seems to be more applicable for long-range connections. However, probabilistic tractography is assumed to be more effective when encountering regions with fiber crossing (Khalsa, Mayhew, Chechlacz, Bagary, & Bagshaw, 2013). Since the integrity of white matter tracts is supposed to decrease with age, which could increase noise within a voxel, it can be argued that this method could also handle tracts with lower integrity better. In addition, we only intended to trace a relatively short segment of the cingulum bundle. Therefore, a probabilistic tractography was conducted using FSL (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). More precisely, FMRIB Software Library's (FSL) BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) and consecutively probtrackx2 were used to calculate the distribution of fiber orientations at each brain voxel and to initiate probabilistic tractography from each voxel within the seed ROI. FSL's tractography tool has the additional advantage of being scriptable, which is crucial when analyzing big data sets (see chapter 4.4).

4.3.2 FUNCTIONAL ANALYSIS

Functional MRI (fMRI) analysis offers a method to investigate neuronal activity in vivo and depends on the principle that increased neuronal activity in a brain region is accompanied with increased blood flow, leading to a hemodynamic response. Additionally, the indirect measure of neuronal activity is based on the fact that oxygenated and deoxygenated hemoglobin have different magnetic properties. Thus, the proportion of change between oxygenated and deoxygenated hemoglobin can then be measured and is called the blood oxygenated level-dependent (BOLD) signal.

Typically, participants are provided with a task in the scanner during which the change over time of the BOLD signal within voxels is collected to analyze localized task-specific neuronal activity. It is only recently that resting-state functional connectivity (rs-fMRI) analysis has gained in popularity, which makes it possible to study human brain function when participants are at rest, not performing any specific task.

4.3.2.1 RESTING-STATE FUNCTIONAL CONNECTIVITY

For a long time, the slow spontaneous fluctuation (<0.1Hz) within the fMRI signal measured between breaks of a task has been seen as "noise". It only gained in importance after Biswal and colleagues (1995) found that spontaneous BOLD signal changes were significantly correlated between the bilateral somatosensory cortex regions. The importance of the investigation of resting-state networks was further emphasized since only little change in energy consumption (~5%) was apparent between rest and task engagement of the brain (Raichle & Mintun, 2006). Different research groups have replicated this finding and several networks, each consisting of multiple brain regions showing synchronous low frequency fluctuations, have been identified reliably at rest (van den Heuvel & Hulshoff Pol, 2010). As the brain is never truly at rest, the term resting-state fMRI can be misleading and was only recently referred to as task-free MRI and the networks as intrinsic connectivity networks (D. T. Jones et al., 2012). However, in this thesis we will still retain the still more common term "resting-state".

Since there is growing interest in analyzing functional connectivity, the number of tools available to describe spontaneous BOLD signals has tremendously increased in the last years. Two widely applied methods (i.e., seed-based correlation analysis and independent component analysis) are described in the following paragraph.

Seed-based connectivity examines the BOLD signal correlations (functional connectivity) between a small number of brain regions of interest (ROIs) or individual voxel locations, with

clear a priori hypotheses. In a first step, BOLD signal time series are extracted for the ROI and used as a regressor in a linear correlation analysis to derive whole-brain, voxel-wise functional connectivity maps. Next to whole-brain analyses, the seed-based approach is often applied to investigate the functional connectivity between two a priori defined ROIs. If the time series show a high positive correlation, the voxels/regions are referred to as functionally coupled. This method stands out by its straightforward interpretability but is mostly criticized because of the required a priori declaration of the seed ROI by the researcher. In contrast, the independent component analysis (ICA) depicts a model-free, data driven method, which had gained prominence in resting-state fMRI analysis. The technical details of this method would go beyond the scope of this short introduction but generally, the ICA algorithm estimates statistically independent components from a linearly mixed source (fMRI data). ICA analyses are mostly used when describing temporal and spatial characteristics of entire resting-state networks. A clear advantage of this method, next to the absence of a priori spatial assumptions, is the capability to subtract physiological noise from the data. However, limitations for ICA analyses are difficulties in interpretation of resulting independent components since they can also reflect parts from decomposed networks (depending on the model order dimensionalities). Thus, misclassification of components can occur (Cole, Smith, & Beckmann, 2010).

In this dissertation we were interested in the functional connectivity between the posterior cingulum cortex (PCC) and the medial prefrontal cortex (mPFC), two regions of the well-studied default mode network (DMN). Because we were not interested in the entire DMN, and had a clear a priori hypothesis, the seed-based approach was chosen as the appropriate method to analyze the data. Therefore, the Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Chao-Gan & Yu-Feng, 2010) and the Resting-State fMRI Data Analysis Toolkit (REST; http://www.restfmri.net) (X.-W. Song et al., 2011) were used for

calculation of the functional connectivity maps and for extraction of the BOLD time course for both ROIs.

4.4 HANDLING BIG DATA

Especially in the field of neuroimaging, studies investigate relatively small samples with N ~50. This can be mostly attributed to the fact that big data collections are expensive (e.g., MRI access) and time consuming. Only recently, sample sizes started to increase which was mostly driven by the following reasons. First, small samples are only able to detect large effects and might therefore miss subtle but important outcomes. Second, several statistical methods (e.g., structural equation modeling) need a large sample size. Such approaches are of great interest since they offer the possibility to investigate growth curves and causality rather than correlation per se. Furthermore, the development of software packages, with automatic analysis pipelines for neuroimaging data, offers new possibilities to evaluate data sets of over 100 participants.

An increase in data recording is also found for behavioral measures. In addition, information on several topics like a person's leisure time activities, health, medication, sleep, and nutrition are collected to gain knowledge about the inter-individual variability of participants. Thus, databases are designed to comprise extensive material about each participant. Especially in aging research, such elaborated databases are of incredible value since aging contains and relies on many facets.

However, there are also several difficulties attributed to big data sets.

First, with the increase in data volume by collecting not only one or two but several MRI sequences per participant, separate data servers have to be hired or acquired since local storage space is usually insufficient. In addition, data has to be stored in a very systematic way, thus, extensive databases have to be created and maintained which can be time-consuming and costly. By analyzing big data sets, one prefers software, which is fully

automated. Since an automated workflow has several advantages, such as higher reproducibility and objectivity, compared to manual or semi automated procedures, this is not a draw back but clearly influences the choice of methods used for data analysis. Additionally, since manual interaction is avoided to achieve higher reproducibility, failure from an automated pipeline will not be corrected, which could lead to more excluded participants.

5 EMPIRICAL PART

5.1 STUDY 1: RELATIONSHIP BETWEEN CEREBRAL MACRO- AND MICROSTRUCTURAL WHITE MATTER CHARACTERISTICS AND EXECUTIVE FUNCTIONS IN HEALTHY OLDER ADULTS[1]

5.1.1 INTRODUCTION

Aging is associated with both macro- and microstructural white matter changes (Gunning-Dixon, Brickman, Cheng, & Alexopoulos, 2009; Madden et al., 2012). It has been hypothesized that these neuroanatomical alterations are related to or mediate age-related cognitive changes, particularly executive functioning (EF) and processing speed (PS) (Fjell & Walhovd, 2010; Raz & Rodrigue, 2006).

While the relationship between PS and white matter characteristics is comparably well described, relating white matter characteristics to EF seems more difficult mainly because of the substantial inconsistencies in the definition and conceptualization of EF and its subcomponents (e.g., Miyake et al., 2000). Thus, the interpretation of the neuropsychological tests selected to test EF in the context of white matter alterations differs over studies. In addition, even though it has been shown that the different EF-subcomponents are associated with different neuroanatomical white matter structures (Kennedy & Raz, 2009), previous studies often combine various EF-subcomponents into a single compound score (e.g., He, Wong, et al., 2012; Vernooij et al., 2009). However, this is problematic in terms of conceptualizing EF. In this study we will rely on the concepts designed by Miyake et al. (2000) who demonstrated that three basic psychological functions best describe the core

[1] A similar version of this study has been submitted for publication to Brain Structure & Function (Hirsiger, Mérillat, Erdin, Koppelmans, Narkhede, Brickman, & Jäncke)

elements of EF: inhibition, shifting, and updating. Additionally, processing speed scores will be assessed for reference measuring general age-related slowing.

Regarding white matter measures, studies investigating the relationship between white matter and cognition usually report either macrostructural (e.g., volume) or microstructural white matter integrity (Kennedy & Raz, 2009; O'Sullivan et al., 2001; Prins et al., 2005). White matter microstructural integrity is described by diffusion of water molecules within WM. Using diffusion tensor imaging (DTI) several values can be specified based on directionality and quantity of water motion. These include: fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) (Mori & Zhang, 2006). Of those studies that reported on microstructural white matter properties the majority only evaluated FA and sometimes MD, but did not report on RD and AD which could provide additional information since RD is commonly associated with myelin integrity, while AD is assumed to reflect axonal integrity (S.-K. Song et al., 2003). In turn, studies that investigated macrostructural white matter properties often focus on either white matter volume, or white matter hyperintensities (WMH). It is hypothesized that WMH are caused by myelin degeneration and small vessel loss (Murray et al., 2012). It is further suggested that white matter degeneration progresses continuously with WMH depicting the most advanced stage (Maillard et al., 2013). Typically, macrostructural white matter properties have not been combined with microstructural white matter outcome measures.

The few studies that did report diffusion metrics separately for white matter outside and inside the WMH in relation to cognition (Jokinen et al., 2013; Schmidt et al., 2010; Vernooij et al., 2009) showed that the relationship between cognitive abilities was different for microstructural integrity outside and within hyperintense WM. These findings emphasize the importance to distinguish between white matter integrity within and outside WMH since investigating white matter microstructural integrity within WMH gave supplementary

information in addition to WMH volume. In this study we will combine fluid-attenuated inversion recovery (FLAIR) and DTI sequences to describe the severity of white matter integrity loss within WMH. In addition, associations between behavioral measures and WMH will be evaluated since relations may be distinct depending on the stage of damage within WMH.

Based on data from a large, well-educated non-demented sample of older participants the goal of this study was to provide new insights in cognitive control in senescence by investigating the association between both, macro- and microstructural white matter properties and well-defined EF-subcomponent measures (i.e., inhibition and task-switching). We hypothesize that white matter microstructural integrity is lower within WMH than within the NAWM. Based on previous literature we hypothesize that cognitive performance is positively associated with NAWM volume and white matter integrity within NAWM and WMH, but negatively with WMH volume. Along this line we hypothesize that not solely the volume but also the state of damage within a WMH is associated with cognitive deterioration. With this distinction of white matter microstructural integrity within WMH and NAWM in combination with well-defined cognitive measures we aim to attain a deeper knowledge about the macro- and microstructure of white matter and cognitive functioning in healthy aging.

5.1.2 Materials and Methods

Participants

This study is based on data from the first wave of the longitudinal healthy aging brain (LHAB) database project, a longitudinal study conducted at the International Normal Aging and Plasticity Imaging Center (INAPIC) in Zurich, Switzerland (Zöllig et al., 2011). The study sample consisted of 200 participants with a mean age of 70.54 ± 4.88 years (106 women 94 men) who had complete data for DTI, FLAIR images, education and blood pressure.

Participants were recruited through the university for seniors in Zurich and two local newspaper advertisements. Subjects had to fulfill the following inclusion criteria: age>64, Mini-Mental State Examination (MMSE; M. F. Folstein et al., 1975) score>26, German native speaker, right-handed, no self reported history of neurological/psychiatric disease, and no contraindications for MRI. The local ethics committee approved the study and all participants gave written informed consent.

NEUROPSYCHOLOGICAL TESTS

Inhibition performance was assessed using a computerized version of the Stroop task (Vienna Test System, Schuhfried). Hundred word stimuli (25 congruent, e.g., "red" displayed in red letters, and 75 incongruent words, e.g., "red" displayed in blue letters) were randomly presented on a screen. The participants were instructed to indicate the color in which the letters were displayed as fast as possible by pressing the corresponding color button. Median reaction times for the congruent stimuli (RT_C) and for the incongruent stimuli (RT_I) were compared. A difference score for inhibition performance (IP_{Diff}) was computed (RT_I–RT_C). In addition, a ratio score (IP_{Ratio}) was calculated (RT_I/RT_C). A ratio score, in contrast to a difference score, is supposed to account more precisely for general age-related slowing. According to Graf et al. (1995) a ratio score reflects a better estimation of the unique interference ability as RT_I and RT_C are differentially affected by general age-related slowing which is expected to behave exponentially with task difficulty (Graf et al., 1995; Troyer, Leach, & Strauss, 2006; Verhaeghen & De Meersman, 1998).

Task-switching performance was measured using the Trail Making Test (TMT; Reitan & Wolfson, 1985), which consist of two parts. In part A (TMT-A) the goal is to connect ascending numbers in the correct order as fast as possible. In part B (TMT-B) in contrast to TMT-A, not only numbers but also letters have to be connected alternately (e.g., 1, A, 2, B, …). In this study we analyze the scores from TMT-B and a difference score (TMT_{Diff}=TMT-

B–TMT-A) separately. Both scores are frequently reported as measures of task-switching or EF respectively (Jacobs et al., 2011; Jokinen et al., 2013). Additionally, the reaction time RT_C and performance in TMT-A were analyzed as reference measures to further differentiate between EF and processing speed performance.

MRI ACQUISITION

MRI was performed on a Philips Ingenia 3T scanner. For structural imaging, two T1-weighted (T1) scans were collected in a sagittal plane with a 3D Turbo-Field-Echo (TFE) sequence (TR=8.18ms, TE=3.799ms, field of view (FoV)=240×240 mm, acquisition matrix=240×240mm, slice thickness=1mm, 160 slices, $1mm^3$ isotropic voxel, flip angle=8°, number of signal average (NSA)=1, duration~7:30min.). The DTI scan consisted of a single-shot echo-planar (EPI) sequence (TR=23'983ms, TE=55ms, FoV=224×224mm, acquisition matrix=112×112mm, slice thickness=2mm, 75 contiguous slices, $2mm^3$ isotropic voxel, flip angle=90°, Echo Train Length (ETL)=59, NSA=1). One non-weighted image (b value=$0s/mm^2$), and 32 diffusion-weighted directions with a maximum b-value of $1000s/mm^2$ were obtained. The diffusion-weighted directions were equally distributed in space. Acquisition time was ~15min. The WMH-volume was estimated (see below) from a fluid-attenuated inversion recovery (FLAIR) sequence (TR=11'000ms, TE=125ms, TI=2'800, FoV=240×180mm, acquisition matrix =368×186, slice thickness=4mm, 32 slices, voxel size=0.65×0.97×$4mm^3$, NSA=1, scan time ~2min).

IMAGE PREPROCESSING

DTI images were processed with FMRIB's diffusion toolbox (FDT) (FMRIB Software Library (FSL); http://fsl.fmrib.ox.ac.uk/fsl/fslwiki) (Smith et al., 2004) by executing the following steps. First, data were corrected for head motion artifacts and eddy currents. Second, a binary brain mask was created based on the first recorded non-diffusion weighted

(b=0) image with FSL's brain extraction tool (BET) applying a fractional intensity threshold of 0.3.

Diffusion tensors were fitted locally at each voxel using dtifit, which yielded fractional anisotropy (FA), mean diffusivity (MD) and axial diffusivity (AD) images. In addition, a Radial Diffusivity (RD) map was computed.

T1 images were averaged using FSL's *AnatomicalAverage* script. Prior to averaging, all T1 images were neck-stripped (under the cerebellum) to enhance averaging accuracy.

Magnetic field inhomogeneity artifacts were corrected within the brain area of the averaged T1 and FLAIR images by applying N4ITK (Tustison et al., 2010) within a binary brain mask obtained by FSL's BET with a fractional intensity threshold of 0.3 and robust brain center estimation.

WHITE MATTER HYPERINTENSITIES

WMH volume was calculated according to an adapted version of the quantification approach developed in house (Brickman et al., 2009; 2011). Briefly, a voxel intensity histogram of each individual FLAIR image was compiled. After fitting Gaussian curves to these distributions, the mean and standard deviation of the intensities were derived. In this study sample, WMH were defined as those voxels with an intensity higher than 1.7 x standard deviation above the mean. After applying the threshold, all images were further inspected visually and errors were corrected manually by two of the authors (CE and AN).

TOTAL WHITE MATTER

To assess the volume of cerebral white matter we used FreeSurfer (http://surfer.nmr.mgh.harvard.edu) to first construct a cerebrum mask by subtracting FreeSurfer's cerebellum, brainstem and 4th ventricle maps from FreeSurfer's binarized white matter parcellation map (wmparc). The resulting image was dilated and holes that did not touch the edge of the FoV were filled. Finally, FreeSurfer's white matter segmentation map

(wm.seg) was masked with the cerebrum mask and an intracranial volume (ICV) mask that was created by combining FSL's BET and tissue class segmentations to obtain a binary map of the cerebral white matter.

DTI PARAMETERS WITHIN THE WMH AND THE NAWM

First, FLAIR images were rigidly registered to the T1 images using FMRIB's Linear Image Registration Tool (FLIRT) with mutual information used as cost function. The transformation matrix was then applied to the WMH maps with nearest neighbor interpolation. Second, skull striped MD and T1 images were co-registered with the same FSL command and options used for the FLAIR image. The acquired transformation matrix was then applied to the other DTI images. Both registrations were visually checked. The MD map was chosen as the reference image since it was previously shown to yield optimal registration results (Vernooij et al., 2009).

Mean voxel DTI parameters of white matter either within the WMH or the NAWM were calculated by first masking all diffusion images with both the WMH and the cerebral white matter mask, respectively, and subsequently extracting the mean voxel DTI parameters from the masked DTI images.

For an overview of the preprocessing and masking steps please see Figure 3.

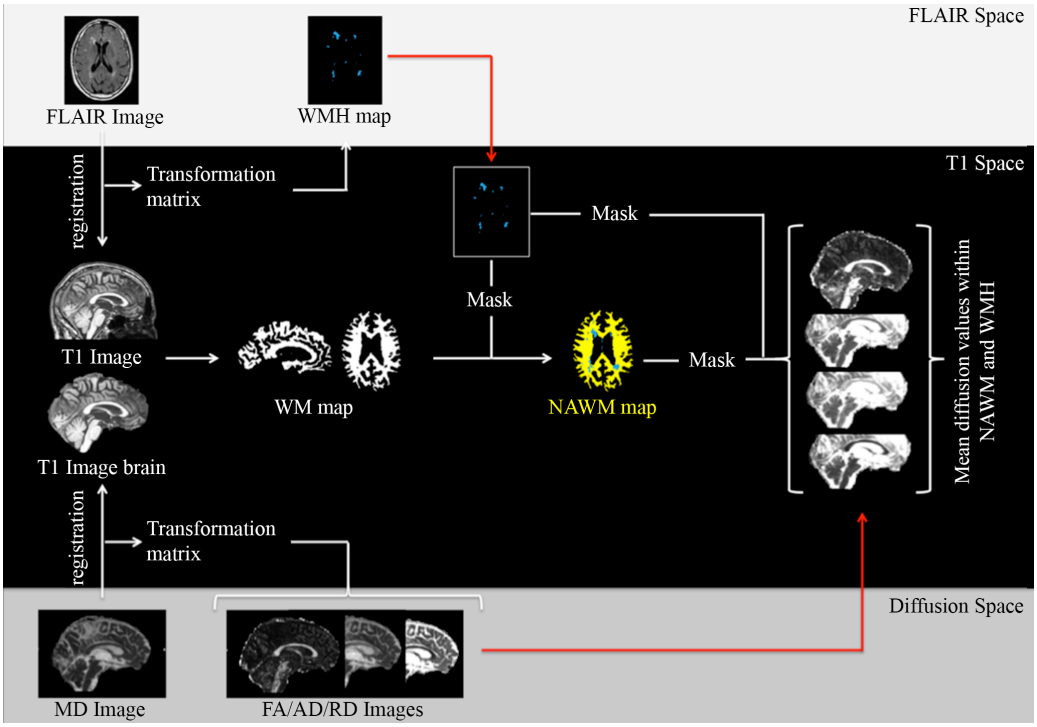

Figure 3. Overview of the registration process
Abbreviations: AD=axial diffusivity; FA=fractional anisotropy; MD=mean diffusivity; NAWM=normal appearing white matter; RD=radial diffusivity; WM=white matter; WMH=white matter hyperintensities

STATISTICAL ANALYSIS

Data analysis was conducted using IBM SPSS Statistics for Mac OS X, Version 19.

For dependent and independent variables data three standard deviations (SD) above or below the mean (M) were considered as outliers and removed from the analysis in order to prevent that these cases drive the associations.

WMH volumes were natural log-transformed because of skewness. In addition, all variables of interest (i.e., micro- and macrostructural white matter measures, different EF and PS scores) were standardized using z-scores for better comparisons between tests and brain parameters. First, the relationships between age and cognition measures were evaluated using Pearson correlations. General linear models (GLM) were conducted to analyze the relationship between age and white matter characteristics. Models were adjusted for gender, education and diastolic blood pressure. Models were additionally corrected for ICV if

NAWM volume or WMH volume were present in the model. The same approach was chosen to analyze the relations between white matter macrostructural and microstructural measures. To analyze if microstructural integrity within and outside WMH differ we used dependent two-tailed t-tests. Further, when analyzing the association between cognitive performance (dependent variable) and diffusion measures three different GLMs were conducted: (1) without adjustment; (2) adjusted for age, gender, education and diastolic blood pressure; and (3) the same as model 2 but additionally adjusted for NAWM and WMH volume to control for white matter atrophy and WMH burden. All models were additionally adjusted for ICV if associations with NAWM or WMH volume were analyzed. The level of significance for all tests was set to p=.05, uncorrected for multiple comparisons unless otherwise indicated.

COVARIATES

Statistical analysis was controlled for the following variables, which are associated with aging, cognitive performance, white matter integrity and/or head size: gender, education and blood pressure. Years of education were determined by self-report at the beginning of the neuropsychological assessment. Blood pressure was measured three times on the same day while subjects were seated and in upright position with the arm at rest using a blood pressure cuff (Model M6, HEM-7211-E; Omron Corporation, Kyoto, Japan). The average diastolic blood pressure was used for analysis. Further, ICV was obtained by FreeSurfer (estimated total ICV).

5.1.3 RESULTS

Demographic characteristics of the study participants are presented in Table 1. EF-subcomponents scores and PS measures were all significantly associated with age (IP_{Diff}: r(195)=.24; IP_{Ratio}: r(196)=.21; TMT-B: r(193)=.36; TMT_{Diff}: r(193)=.22; RT_C: r(195)=.31; TMT-A: r(194)=.25 (p range<.001-.003)).

Table 1. *Demographic Characteristics of the Study Participants*

Variable	N	M (SD)
Age	200	70.54 (4.88)
Men (n (%))	200	94 (46%)
Education Years	200	14.63 (3.37)
Blood Pressure diastolic (mmHg)	200	81.35 (10.02)
MMSE	200	28.87 (0.99)
Cognitive Measures		
Stroop Naming Test:		
RT_C (sec)	197	0.98 (0.16)
IP_{Diff} (sec)	197	0.11 (0.10)
IP_{Ratio}	198	1.11 (0.09)
Trail Making Test:		
TMT-A (sec)	196	37.36 (11.05)
TMT-B (sec)	195	51.74 (23.84)
TMT_{Diff} (sec)	195	90.27 (28.43)
White Matter Measures		
NAWM Volume (ml)	200	462.40 (54.90)
WMH Volume (ml)	197	Median 2.39 (3.45)
FA		
NAWM	197	3.3×10^{-1} (1.5×10^{-1})
WMH	199	2.7×10^{-1} (3.3×10^{-2})
MD		
NAWM	196	8.1×10^{-4} (2.8×10^{-5})
WMH	198	1.3×10^{-3} (1.3×10^{-4})
AD		
NAWM	197	1.1×10^{-3} (2.8×10^{-5})
WMH	198	1.6×10^{-3} (1.4×10^{-4})
RD		
NAWM	196	6.7×10^{-4} (3.0×10^{-5})
WMH	198	1.1×10^{-3} (1.3×10^{-4})

Abbreviations: AD=axial diffusivity; FA=fractional anisotropy; IP_{Diff}=inhibition performance difference score; IP_{Ratio}=inhibition performance ratio score; M=mean; MD=mean diffusivity; ml=milliliter; mmHg=millimeter of mercury; MMSE=mini-mental state examination; NAWM=normal appearing white matter; RD=radial diffusivity; RT_C=median reaction time for congruent stimuli; SD=standard deviation; sec=seconds; TMT-A=trail making test part A; TMT-B=trail making test part B; TMT_{Diff}=trail making test difference score; WMH=white matter hyperintensity

With respect to white matter characteristics, we found that both, NAWM and WMH volumes, were significantly associated with age (see Table 2). Further, age was significantly related to all diffusion metrics within the NAWM whereas no correlation was found between the DTI metrics within the WMH. In addition, diffusion properties within NAWM and WMH differed significantly (see Table 2).

Table 2. *Association between Age and White Matter Characteristics*

			Age			t-test (t)[d]
	Parameters	**N**	**β**	**95% CI**	**p**	
	NAWM Vol[b]	200	-.069	-.088; -.049	<.001	
	WMH Vol[b,c]	197	.052	.024; .080	<.001	
FA						
	NAWM[a]	197	-.041	-.069; -.012	.005	25.140**
	WMH[a]	199	.015	-.014; .044	.298	
MD						
	NAWM[a]	196	.100	.075; .126	<.001	-48.030**
	WMH[a]	198	.011	-.018; .040	.440	
AD						
	NAWM[a]	197	.110	.086; .134	<.001	-49.092**
	WMH[a]	198	.023	-.006; .052	.120	
RD						
	NAWM[a]	196	.090	.064; .116	<.001	-45.456**
	WMH[a]	198	.005	-.024; .034	.755	

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; NAWM Vol=normal appearing white matter volume; RD=radial diffusivity; WMH Vol=white matter hyperintensity volume
**p<.01
β values represent the increase in standard deviation in white matter characteristics with one year increase in age
a) adjusted for gender, education, diastolic blood pressure; b) additionally adjusted for intracranial volume; c) natural log transformed; d) t-tests are Bonferroni-corrected for multiple comparisons by using the procedure suggested by Holm (1979)

Table 3 depicts the mutual associations between the different white matter characteristics. More precisely, we found that larger NAWM and smaller WMH volumes were related to lower MD/AD/RD values and to higher FA values measured within the NAWM. When analyzing the relationship between NAWM and WMH volumes and diffusion properties within the WMH, we found that both; NAWM and WMH volumes were negatively associated with MD/AD/RD.

Table 3. *Associations between White Matter Characteristics*

Variable		NAWM Vol[a]	WMH Vol[a,c]	NAWM FA[b]	NAWM MD[b]	NAWM AD[b]	NAWM RD[b]	WMH FA[b]	WMH MD[b]	WMH AD[b]
NAWM Vol	β 95% CI									
WMH Vol	β 95% CI	-.062 -0.164; 0.039								
NAWM FA	β 95% CI	**.101*** 0.004; 0.198	**-.215*** -0.351; -0.080							
NAWM MD	β 95% CI	**-.135*** -.0245; -0.024	**.281**** 0.127; 0.434	**-.846**** -0.956; -0.736						
NAWM AD	β 95% CI	**-.133*** -0.251; -0.015	**.236*** 0.072; 0.401	**-.482**** -0.640; -0.325	**.980**** 0.915; 1.046					
NAWM RD	β 95% CI	**-.128*** -0.234; -0.022	**.281**** 0.134; 0.428	**-.947**** -1.032; -0.862	**.951**** 0.926; 0.976	**.912**** 0.819; 1.004				
WMH FA	β 95% CI	.060 -0.034; .0155	.055 -0.079; 0.188	.132 -0.010; 0.274	-.098 -0.262; 0.067	-.083 -0.256; 0.089	-.087 -0.246; 0.072			
WMH MD	β 95% CI	**-.152*** -0.250; -0.055	**-.181*** -0.319; -0.042	.023 -0.122; 0.168	.128 -0.036; 0.291	**.229*** 0.060; 0.399	.073 -0.086; 0.232	**-.470**** -0.596; -0.344		
WMH AD	β 95% CI	**-.163*** -0.261; -0.064	**-.151*** -0.293; -0.101	.040 -0.105; 0.186	.125 -0.038; 0.289	**.241*** 0.073; 0.409	.067 -0.092; 0.226	**-.194*** -0.334; -0.053	**.954**** 0.910; 0.998	
WMH RD	β 95% CI	**-.140*** -0.237; -0.043	**-.188*** -0.325; -0.051	.012 -0.133; 0.157	.123 -0.041; 0.287	**.213*** 0.044; 0.383	.073 -0.086; 0.232	**-.603**** -0.717; -0.490	**.986**** 0.962; 1.009	**.889**** 0.832; 0.955

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; NAWM Vol=normal appearing white matter volume; RD=radial diffusivity; WMH Vol=white matter hyperintensity volume

*p<.05; **p<.01

β values represent the effect of the variable depicted on the left (row) adjusted for a) age, gender, education, diastolic blood pressure, intracranial volume and b) gender, education, diastolic blood pressure; c) natural log transformed

No associations were found between white matter characteristics (diffusion/volume) and inhibition performance (IP_{Diff}/IP_{Ratio}). Associations between task-switching performance and white matter characteristics are summarized in Table 4. Both task-switching scores were positively associated with NAWM volume and negatively with WMH volume. With respect to diffusion, only the time to complete TMT-B (longer time-on-task indicates worse performance) but not the difference score was significantly positively associated with MD/AD/RD values within NAWM. Within hyperintense WM, MD was positively related to $TMT_{Diff,}$ while AD was positively associated with both task-switching measures. After adjustment for covariates (model 2) and additional adjustment for general white matter atrophy (model 3), only the associations between performance and NAWM volume, and between performance and the MD/AD within WMH remained significant.

Associations between PS scores and white matter characteristics are presented in Table 5. For model 1, both measures were associated with NAWM Volume but only RT_C was related to WMH Volume. TMT-A completion time and RT_C were significantly positively associated with MD/AD/RD values within NAWM, while FA was additionally negatively related to RT_C. No associations were found for diffusion metrics within WMH and PS scores. In model 2, significant relations were still present between a) RT_C and NAWM volume (negative relationship), b) RT_C and MD/AD/RD within NAWM (positive relationship), and c) TMT-A and AD within NAWM (positive relationship). After additional adjustment for WMH and NAWM volume the positive associations between RT_C and MD/AD as well as between TMT-A completion time and AD remained significant.

Table 4. *Effects of White Matter Characteristics on Task-Switching Performance*

		Model 1		Model 2		Model 3	
		TMT-B	**TMT_{Diff}**	**TMT-B**	**TMT_{Diff}**	**TMT-B**	**TMT_{Diff}**
NAWM Vol[a]	β 95%CI	**-.445**** -.620; -.273	**-.377**** -.553; -.200	**-.273*** -.467; -.080	**-.300*** -.502; -.098		
WMH Vol[a,b]	β 95%CI	**.181*** .036; .326	**.156*** .011; .301	.100 -.041; .241	.111 -.036; .259		
NAWM							
FA	β 95%CI	-.052 -.198; .095	-.019 -.162; .125	.018 -.120; .156	.030 -.112; .172	.057 -.086; .199	.082 -.063; .226
MD	β 95%CI	**.232*** .087; .378	.096 -.048; .241	.110 -.047; .267	.021 -.140; .181	.064 -.102; .229	-.029 -.197; .139
AD	β 95%CI	**.256**** .114; .398	.107 -.037; .250	.142 -.020; .304	.033 -.134; .200	.101 -.069; .272	-.007 -.182; .168
RD	β 95%CI	**.205*** .059; .351	.086 -.058; .231	.086 -.067; .238	.014 -.142; .170	.040 -.120; .199	-.037 -.198; .125
WMH							
FA	β 95%CI	.036 -.105; .177	.037 -.104; .178	.013 -.118; .144	.025 -.113; .162	.023 -.107; .153	.033 -.103; .168
MD	β 95%CI	.132 -.008; .272	**.153*** .014; .292	.109 -.022; .240	**.141*** .004; .278	.090 -.053; .233	**.148*** .000; .296
AD	β 95%CI	**.171*** .032; .311	**.195*** .056; .333	**.132*** .000; .263	**.174*** .037; .310	.114 -.031; .258	**.186*** .037; .336
RD	β 95%CI	.105 -.035; .245	.124 -.016; .264	.092 -.039; .224	.118 -.019; .255	.073 -.068; .241	.120 -.026; .267

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; NAWM Vol=normal appearing white matter volume; RD=radial diffusivity; TMT-B=trail making test part B; TMT_{Diff}=trail making test difference score; WMH Vol=white matter hyperintensity volume

*p<.05; **p<.01

Higher task-switching scores depict poorer performance

β values represent the increase in standard deviation (SD) in task-switching performance with 1 SD increase in white matter characteristics

Model 1: non-adjusted. Model 2: adjusted for age, education, gender and diastolic blood pressure. Model 3 same as Model 2, additionally adjusted for NAWM Vol and WMH Vol

a) additionally adjusted for intracranial volume; b) natural log transformed

Table 5. *Effects of White Matter Characteristics on Processing Speed Performance*

		Model 1		Model 2		Model 3	
		TMT-A	**RT_C**	**TMT-A**	**RT_C**	**TMT-A**	**RT_C**
NAWM Vol[a]	β 95%CI	**-.251*** -.432; -.070	**-.336*** -.515; -.157	-.120 -.327; .086	**-.213*** -.416; -.010		
WMH Vol[a,b]	β 95%CI	.131 -.015; .277	**.161*** .019; .302	.059 -.091; .209	.101 -.044; .246		
NAWM							
FA	β 95%CI	-.047 -.192; .099	**-.188*** -.327; -.049	-.004 -.141; .148	-.126 -.264; .011	.015 -.138; .098	-.071 -.215; .073
MD	β 95%CI	**.224*** .077; .371	**.292**** .156; .428	.157 -.008; .323	**.211*** .057; .365	.130 -.049; .308	**.169*** .005; .333
AD	β 95%CI	**.271**** .127; .415	**.315**** .181; .450	**.226*** .056; .396	**.248*** .088; .408	**.199*** .016; .382	**.232*** .062; .402
RD	β 95%CI	**.187*** .040; .334	**.267**** .130; .403	.115 -.046; .275	**.182*** .032; .332	.089 -.084; .261	.132 -.027; .290
WMH							
FA	β 95%CI	-.006 -.151; .139	-.050 -.191; .091	-.019 -.160; .122	-.072 -.208; .063	-.011 -.154; .132	-.062 -.197; .072
MD	β 95%CI	.057 -.086; .199	.112 -.030; .254	.046 -.094; .186	.102 -.035; .239	.014 -.142; .170	.126 -.023; .275
AD	β 95%CI	.069 -.072; .211	.116 -.026; .257	.047 -.093; .186	.088 -.050; .225	.009 -.147; .165	.107 -.044; .257
RD	β 95%CI	.048 -.095; .191	.106 -.036 to.248	.045 -.096; .185	.106 -.030; .243	.016 -.139; .170	.129 -.018; .277

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; NAWM Vol=normal appearing white matter volume; RD=radial diffusivity; RT_C=median reaction time for congruent stimuli; TMT-A=trail making test part A; WMH Vol=white matter hyperintensity volume
*p<.05; **p<.01
Higher processing speed scores depict poorer performance
β values represent the increase in standard deviation (SD) in processing speed performance with 1 SD increase in white matter characteristics
Model 1: non-adjusted. Model 2: adjusted for age, education, gender and diastolic blood pressure. Model 3 same as Model 2, additionally adjusted for NAWM Vol and WMH Vol
a) additionally adjusted for intracranial volume; b) natural log transformed

5.1.4 DISCUSSION

Analyses of macro- and microstructural white matter characteristics assessed at the first time point of the Zurich LHAB database project confirm the well-established effects of white matter atrophy (Fjell & Walhovd, 2010) and increasing WMH burden with age (Breteler et al., 1994; de Groot et al., 2000; Gunning-Dixon & Raz, 2003).

By combining different imaging modalities (DTI and FLAIR) we found according to our hypothesis that white matter microstructural integrity within WMH was generally lower compared to that within the NAWM. Additionally, our results indicate that diffusion metrics within NAWM and WMH are differently related to variables such as age. While we do find associations of age and diffusion metrics within NAWM, those are not present in hyperintense WM. Whether this suggests that white matter integrity within the WMH does not change with age or if this finding can be ascribed to our very healthy sample needs to be investigated in future longitudinal studies. The disparity between WMH and NAWM found in this study emphasizes the importance of separating the two tissue types when analyzing white matter characteristics in the aging brain. However, simply thresholding the diffusion measures using an arbitrary value to discriminate between NAWM and WMH does not seem appropriate since the range of diffusion values within NAWM and WMH overlap. In contrast, combining multimodal imaging enables the separation of NAWM and WMH in an appropriate manner.

To gain further insight into the brain-behavioral relationship in healthy aging we combined different white matter macrostructural and microstructural measures with cognitive performance. Our results support our hypothesis that cognition is generally positively associated with NAWM volume and white matter integrity within NAWM and WMH. For executive functions our results showed that similar to former DTI studies (Grieve, Williams, Paul, Clark, & Gordon, 2007; Jokinen et al., 2013; Kennedy et al., 2009; O'Sullivan et al.,

2005) different EF-subcomponents are associated differently with white matter characteristics, which suggest that composite scores for EF should be reconsidered when investigating brain-behavior relationships in order to gain more specific results for the EF-subcomponent tested. After controlling for confounding variables, in contrast to NAWM volume, no significant association could be found between WMH volume and task-switching performance. In addition, no association could be found between DTI metrics within NAWM, which are normally used to investigate brain-behavioral relationships. In comparison, TMT_{Diff} was associated with DTI parameters within WMH, which still reached significance after adjustment for covariates. This finding indicates that rather the severity of damage within a WMH than volume of a WMH is associated with cognitive deterioration.

Given that the association between PS and higher white matter integrity has been repeatedly reported (Fjell & Walhovd, 2010) and considering that many EF tests comprise a PS component (Salthouse et al., 2003) we separately investigated the association between PS performance and white matter characteristics in our dataset. Interestingly, in addition to NAWM volume only diffusion metrics within NAWM were associated with PS performance. Findings were still significant after adjusting for covariates and NAWM/WMH volume. This is in agreement with the aging literature, which states that better PS performance is associated with higher FA and lower MD/AD/RD values, along with lower WMH burden (Gunning-Dixon & Raz, 2000; Jacobs et al., 2011; Kennedy & Raz, 2009; Madden et al., 2004; Prins et al., 2005; Vernooij et al., 2009). Our data showed that PS is positively related to measures of NAWM whereas tasks-switching performance was rather associated with the diffusion metrics within WMH. Contrary to our hypothesis, WMH volume was not related to cognitive measures. This finding is of interest since one could argue that the degree of damage within the WMH, which is indicated by microstructural integrity, is of higher relevance for cognitive functioning than WMH volume alone. In addition, since PS is suggested to be associated to

global white matter deterioration whereas EF is more affected by local white matter integrity decline (Albinet, Boucard, Bouquet, & Audiffren, 2012), investigating the entire cerebrum may have overlaid the association between NAWM and EF. Further, dependent on their location and severity (indicated by lower RD and MD) WMH could have disrupted specific tract organization important for EF functioning. Interestingly, the unadjusted association between TMT-B completion time and white matter characteristics resembles the white matter associations with PS performance, which leads to the conclusion that TMT-B times are likely confounded by generalized age-related slowing.

Nevertheless, some of our findings stand in contrast to former studies demonstrating that EF performance deterioration is associated with loss of white matter integrity and/or increase in WMH severity (Charlton et al., 2008; Grieve et al., 2007; Kennedy & Raz, 2009; Madden et al., 2009; Parks et al., 2011; Soriano-Raya et al., 2014; Zahr, Rohlfing, Pfefferbaum, & Sullivan, 2009). However, due to several methodological differences only few studies can be directly compared to ours. First, EF performance is mostly based on a composite score, which can include a variety of different cognitive tests (e.g., verbal fluency, Digit-Symbol Test). Regarding studies using DTI to investigating the relationship between separate EF-subcomponents and white matter characteristics found results similar to us. O'Sullivan and colleagues (2001) studied the relationship between inhibition/task-switching abilities and white matter diffusion properties (FA, MD) in younger and older subjects on a whole brain level and within three different ROIs (white matter anterior, middle and posterior part). They reported a significant relationship between MD in anterior white matter and task-switching performance (indicated by TMT_{Diff}), but not between diffusion measures and inhibition (measured with the Wisconsin Card Sorting Test (WCST)). Similarly, a recent study by Kennedy and Raz (2009) found no association between the integrity of several white matter tracts and inhibition measured using the WCST. In contrast, by assessing inhibition using the

Stroop task, the authors revealed significant associations with parietal and occipital FA. In addition, the authors also found associations between task-switching tests and the occipital/frontal ROI (FA) and the genu of the corpus callosum/parietal ROI (MD). These findings from Kennedy and Raz (2009) are particular interesting because they suggest that also the test paradigm chosen to assess a particular EF-subcomponent can impact upon the results.

In contrast, we found no association between inhibition performance measured with the Stroop task and white matter characteristics (Kennedy et al., 2009). This could be referable to methodological differences such as sample size and/or age range. The latter might be especially important in aging research, as there is no clear cut from when on participants are "classified" as older. Notably the smaller age range in our study (only analyzing participants>64 years) leads to a more homogenous sample with less variance in the variables of interest compared to studies, which investigate cognitive performance over a broader age range or even contrast results between young and older subjects

More controversial results are found in studies investigating WMH volumes and their relation to cognitive measures (Mortamais et al., 2013). Variability of results could be caused by the different techniques used to assess WMH (e.g., estimated by a neurologist using the Fazekas scale (Fazekas et al., 1987) or using automatic procedures). In addition, different MRI protocols have been used to quantify WMH (FLAIR, T2). Furthermore, the mean extent of the WMH burden differs largely across studies (from a mean of ~ 4ml to ~ 20ml). In our study, with a median of 2.39 ml our participant's white matter seems to be only marginally effected by WMH, which also emphasizes the healthiness of our participants.

Several previous studies investigating the relationship between EF and white matter analyzed both, diffusion metrics and WMH volume (Borghesani et al., 2013; He, Wong, et al., 2012; Jacobs et al., 2011; Jokinen et al., 2013; O'Sullivan et al., 2005; Quinque et al., 2012; Schmidt

et al., 2010; Soriano-Raya et al., 2014; Vernooij et al., 2009). However, from these studies only three analyzed diffusion metrics within WMH, and only Vernooij and colleagues (2009) contrasted diffusion properties in hyperintense white matter to those in NAWM, whereas Schmidt and colleagues (2010) as well as Jokinen et al. (2013) compared diffusion metrics between WMH and normal appearing brain tissue (NABT), which was defined as the sum of gray and white matter outside the WMH. Partly in contrast to our study Vernooij and authors (2009) found that EF performance was associated with NAWM volume, WMH volume and with the majority of diffusion metrics within NAWM and WMH. It is important to consider that EF performance in this study was assessed with a composite score combining results from multiple tests namely the Stroop interference subtask, the letter-digit substitution test (LDST), and the word fluency test. Therefore, it could be argued that tests such as LDST, which have a high PS component, could have driven the effect.

The findings of the present study should be interpreted with the following limitations in mind. First, this is a cross-sectional evaluation and therefore no conclusion about causality can be drawn. Follow-up data that will enable us to investigate causal relationships are currently being collected. In addition, inhibition and PS was measured with a single test. Including multiple measures for inhibition and task-switching could yield a more reliable estimate of this domain and might therefore be a better option. However as stated above, even tests measuring the same EF-subcomponent can lead to different associations when combined to a composite score which could deteriorate findings. Probably the best way to deal with this problem would be to conduct a factor analysis. Since our analysis focused on the difference between DTI measures within and outside NAWM in healthy older participants independent from WMH location we did not differentiate between periventricular and deep WMH. For future work, the influence of the specific location of WMH on brain-behavior relationships (e.g., on the association between DTI metrics within WMH and cognition) might be an

interesting issue to study. In addition, the associations found in this study did not survive a correction for multiple comparisons. However, the fact that we found significant brain-behavioral relations in a very healthy, highly functioning sample within a narrow age range, after controlling for several covariates suggests that our results contribute to a better understanding of the brain-behavioral relationship in healthy aging.

One of the core strength of the reported study is the healthy, highly educated, large and homogenous sample of older participants included in the longitudinal healthy aging brain (LHAB) database project. The rationale of the LHAB database project is to investigate neuroanatomical and functional characteristics related to cognitive outcome measures in healthy aging to gain crucial information about successful aging. The project is characterized by strict exclusion criteria (e.g., MMSE>26) to prohibit participants with risk of mild cognitive impairment (MCI). In addition, we ran our multimodal MRI protocol on a 3T scanner, while previous studies that differentiated between NAWM/NABT and WMH (Jokinen et al., 2013; Schmidt et al., 2010; Vernooij et al., 2009) used MRI scanners with lower field strengths. Higher field strengths are associated with a better signal to noise ratio and higher spatial resolution, which improves image clarity. Masking out the cerebellum further refined our results, since the cerebellum is not strongly associated with EF performance. Furthermore, by using a multimodal approach we were able to accurately segment cerebral white matter into NAWM and WMH and obtain information about diffusion metrics within these classes.

CONCLUSION

By analyzing macro- and microstructural white matter properties within a large and homogenous healthy sample of older adults, we were able to obtain separate measures of microstructural integrity for the cerebral NAWM and WMH. Subsequently, we looked at their relation with age and subcomponents of executive functioning. Our results show that cerebral

NAWM and WMH have clearly different diffusion properties in healthy aging participants and should therefore be distinguished and analyzed separately. This was further supported by different associations between task-switching/PS and DTI metrics within NAWM and WMH. In addition, we showed that distinct EF-subcomponents were differently associated with cerebral white matter properties, thus, arguing against the use of composite scores that comprise more than one EF-subcomponent.

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LJ is a faculty member of the LIFE Course: Evolutionary and Ontogenetic Dynamics.

5.2 STUDY 2: STRUCTURAL AND FUNCTIONAL CONNECTIVITY IN HEALTHY AGING: ASSOCIATIONS FOR COGNITION AND MOTOR BEHAVIOR[2]

5.2.1 INTRODUCTION

It is well established that healthy aging is associated with changes in behavior, neuroanatomical and functional brain metrics (Bennett & Madden, 2014; Ferreira & Busatto, 2013; Fjell & Walhovd, 2010). However, if or how the age-related decline in behavioral measures can be explained by neuroanatomical and/or functional intra-individual differences is still not fully understood. One underlying mechanism for behavioral deterioration as well as for loss of functional connectivity could be described by the disconnection hypothesis (O'Sullivan et al., 2001). The hypothesis is based on Geschwind's proposal of disconnection syndromes (Geschwind, 1965), which suggests the importance of white matter networks for higher order function. Within this framework the decline in cognitive abilities could be related to deterioration of white matter tract integrity due to its impact on communication between brain regions.

Indeed, there is evidence for microstructural deterioration of white matter tracts in old age that seems to be more pronounced in frontal than in posterior brain regions (Bennett & Madden, 2014). In addition, higher-order cognitive abilities such as processing speed, executive functions and episodic memory are reported to be associated with white matter integrity in normal healthy aging (Madden et al., 2012), supporting the disconnection hypothesis.

With the fairly recent development of resting-state functional connectivity it has become possible to study intrinsic functional connectivity between different brain regions when

[2] A similar version of this study has been submitted for publication to Cerebral Cortex (Hirsiger, Koppelmans, Mérillat, Liem, Erdeniz, Seidler, & Jäncke)

participants are at rest, thus removing the confound of strategic task performance effects. Several networks, each consisting of multiple brain regions, have been identified reliably (Fox, Snyder, Vincent, & Raichle, 2007). The default mode network (DMN) is one of the intrinsic resting-state networks that has been most studied with respect to aging. The DMN includes the medial prefrontal cortex, posterior cingulate/retrospinal cortex, inferior parietal lobule and the hippocampus (Buckner, Andrews-Hanna, & Schacter, 2008). These regions are important for cognitive and motor functioning and therefore age-related changes in DMN functional connectivity strength could potentially explain part of the variation in behavioral performance with age (Ferreira & Busatto, 2013). Indeed, several studies have reported decreases in DMN connectivity strength in group comparisons between young and older participants (Dennis & Thompson, 2014) but also a cross-sectional analysis over a larger age range depicted a linear decline of functional connectivity strength over the life span (Onoda et al., 2012). However, a recent longitudinal study investigating participants with a mean age of 65.2 (range 49-79 years) at baseline did not detect any changes in DMN functional connectivity strength after 6 years follow-up (Persson et al., 2014), although they did show that a decrease in default mode connectivity strength was associated with a decline in memory performance.

Considering that white matter tracts depict the anatomical connections for functional connectivity it can be argued that investigating solely structural or functional connectivity provides a limited view of the complexity of the human brain and combined analysis could reveal more information about brain-behavior relationships. Nonetheless, studies investigating the association between structural and functional connectivity are still scant in the field of healthy aging. So far, one study found that integrity of the white matter tract connecting the posterior cingulate cortex (PCC) and hippocampus was associated with functional connectivity strength between the two regions (Teipel et al., 2010). In addition,

functional connectivity strength between the PCC and the medial prefrontal cortex (mPFC) was related with white matter integrity in a larger ROI containing the cingulum bundle (Andrews-Hanna et al., 2007). In addition, after controlling for age, connectivity strength was associated with performance in three domains: memory, executive functioning, and processing speed (Andrews-Hanna et al., 2007). Unfortunately, the association between the underlying white matter integrity and cognitive performance was not analyzed.

To date, it is not clear if the combination of functional and structural connectivity can explain unique variance in cognitive performance in addition to that explained by structural connectivity alone. To answer this question, we analyzed structural and functional connectivity of the cingulum bundle. We chose this specific tract because: a) it anatomically connects two major hubs of the DMN (i.e., PCC and mPFC) and is a DMN connection that is most robustly affected by age (Andrews-Hanna et al., 2007), b) it is reliably traceable (Greicius, Supekar, Menon, & Dougherty, 2009; Khalsa et al., 2013; van den Heuvel, Mandl, Luigjes, & Hulshoff Pol, 2008) and c) white matter integrity within the cingulum is associated with several cognitive outcome measures (psychomotor performance, inhibition and semantic memory) (Metzler-Baddeley et al., 2012). With this methodological approach, our study aims to gain insights into how the structural and functional connectivity of the cingulum bundle together are related to cognition and motor performance in a healthy, well-educated sample of older participants. We hypothesize that there is a relationship between structural and functional connectivity since structural connectivity of the cingulum bundle describes the underlying anatomical connection between the PCC-mPFC functional connectivity (Greicius et al., 2009). Further we hypothesize that cognitive and motor performance is associated with structural connectivity since tests employed in this study were previously related to white matter integrity in healthy aging samples (Bartzokis et al., 2010; Fjell & Walhovd, 2010; Metzler-Baddeley et al., 2012; Zahr et al., 2009) consequently, we suggest that functional

connectivity strength is positively related to behavioral performance. Lastly, the overarching aim of this study was to examine if functional connectivity explains unique variance in behavior in addition to that explained by structural connectivity. We hypothesize that the combination of structural and functional connectivity data will serve as a better predictor for behavioral measures than each connectivity measure separately. By combining structural and functional connectivity measures from a large sample we aim to gain further insight into the relationship between brain and cognition in healthy aging.

5.2.2 MATERIALS AND METHODS

PARTICIPANTS

We sampled 201 subjects from the first time point of the longitudinal healthy aging brain (LHAB) database project conducted at the International Normal Aging and Plasticity Imaging Center (INAPIC) at the University of Zurich, Switzerland (Zöllig et al., 2011) who had complete data for DTI, fMRI, education and blood pressure. Participants were all older than 64, had a Mini-Mental State Examination (MMSE; M. F. Folstein et al., 1975) score higher than 26, had no history of neurological or psychiatric diseases, were right handed and passed MRI safety requirements. All participants gave voluntary informed consent, in accordance with guidelines with the Helsinki declaration, prior to participation.

MRI ACQUISITION

All scans were performed using a 3.0 T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). For each participant, the following images were acquired:

Two high-resolution T1-weighted (T1w) anatomical images using a 3D Turbo-Field-Echo (TFE) sequence with echo time (TE)=3.799ms, repetition time (TR)=8.18ms, field of view (FOV)=240×240mm, acquisition matrix=240×240mm, 160 slices, isotropic voxel size=1 mm^3, flip angle=8°, number of signal average (NSA)=1, duration~7:30 minutes.

Diffusion-weighted single-shot spin echo EPI sequence scans with the following specifications: TE=55ms, TR=23983ms, flip-angle=90°, SENSE factor R=2.0, FOV=224x224mm, voxel size 2x2x2mm, 75 slices, no gap. Diffusion-weighted scans were performed along 32 non-collinear directions with a maximum b-factor of 1000 s/mm^2, complemented by a single b=0 s/mm^2 scan. Acquisition time was ~15 minutes.

T2*-weighted BOLD image parameters were: TR=2s, TE=21ms, flip angle=76°, FOV=220×220mm, voxel size 3.43×3.43×3.5mm, 43 axial slices. For resting-state fMRI 225 volumes were collected within ~8 minutes. Prior to the functional scan, participants were instructed to lay still, relax and to look, but not stare at the fixation cross during data acquisition.

MRI DATA ANALYSIS

T1W IMAGE PREPROCESSING

T1w images were averaged using the *AnatomicalAverage* script from the FMRIB Software Library (FSL) toolbox (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki). The averaged images were corrected for field inhomogeneity using N4ITK (Tustison et al., 2010) within an intracranial mask that was obtained using FSL's brain extraction tool (BET). The bias field corrected averaged image was skull stripped using FSL's BET. For further analysis we refer to this image as the averaged T1w image.

ANALYSIS OF DTI DATA

DTI IMAGE PREPROCESSING

FSL version 5.0.4 was used for eddy current correction and correction of head motion of the diffusion weighted images. FSL's diffusion toolbox was used for tensor fitting to obtain fractional anisotropy (FA), and mean/axial/radial diffusivity (MD/AD/RD) maps (Smith et al., 2004).

PROBABILISTIC TRACTOGRAPHY

We used a seed-based probabilistic approach to track the cingulum bundle. The tractography was therefore conducted between a posterior and anterior ROI. Because the same posterior ROI coordinates were used for the functional and structural analysis, the posterior ROI was placed at the posterior cingulum PCC (MNI coordinate 0, -53, 26) based on a previous resting-state fMRI connectivity study (Van Dijk et al., 2010). However, to ensure that the ROI reached into the WM, which is essential for tractography, we created a spherical ROI with 12mm radius to track the cingulum bundle (vs. 6mm see below). The anterior ROIs for the tractography and resting-state analysis differed. The anterior ROI to track the cingulum was placed in accordance with Wakana et al. (2007). This ROI is situated just above the middle of the genu of the corpus callosum in the coronal plane, a location within WM, which is not suitable for resting-state fMRI analysis. To find the middle of the corpus callosum's genu we first selected the mid-sagittal plane from the genu mask (obtained from the JHU ICBM-DTI-81 White-Matter Labels Atlas). Using *fslstats* the center of gravity was determined indicating the middle of the genu. A box was created with the following dimensions 31x5x30mm. To track the cingulum bundle in the right hemisphere, the left lower corner of the ROI cuboid was placed at 60, 148, 84 (MNI space); for the left cingulum bundle, the left lower corner of the ROI was placed at 90, 148, 84 (MNI space). Both ROIs were used as seed and waypoint masks. Posterior and frontal ROIs are depicted in Figure 4.

For further analyses we transformed the ROIs from MNI into native diffusion space with the following steps:

First, the averaged T1w image was rigidly registered to the DTI images using FSL's Linear Image Registration Tool (FLIRT) with mutual information used as a cost function. The co-registered average T1w image was then normalized into MNI space using linear (FLIRT) and nonlinear registration FNIRT (FSL's Non-linear Image Registration Tool). The obtained

warp-fields were inverted using the invwarp command and subsequently applied to the ROI to obtain the PCC and anterior ROI in native diffusion space.

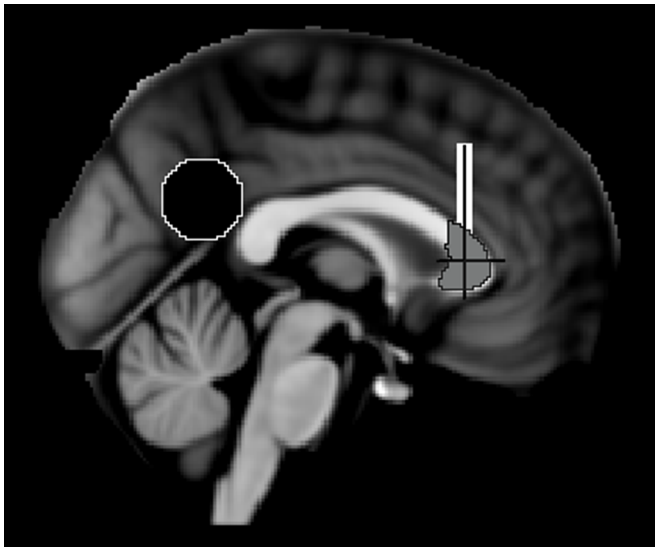

Figure 4. Mid-sagittal image of the MNI152 template brain. Black indicates the posterior cingulate cortex and white the anterior region of interest, gray indicates the genu of corpus callosum. Crosshairs represent the center of gravity of the genu of the corpus callosum

FSL's diffusion toolbox was used to determine the probabilistic tractography. First, we used the BEDPOSTX (Bayesian Estimation of Diffusion Parameters Obtained using Sampling Techniques) command to calculate the distribution of fiber orientations at each brain voxel. Second, the *probtrackx2* command was used to initiate probabilistic tractography from each voxel within the seed ROI. We applied the following parameters: streamlines=25'000; step length=0.5mm; curvature threshold=0.2. To ensure that only the cingulum bundle was tracked, tractography for each hemisphere was conducted twice, once using the PCC ROI as a seed mask and the anterior ROI as a waypoint mask (PCC-tract), and vice versa (i.e., anterior ROI=seed mask; PCC=waypoint mask; anterior-tract). All tracts were further thresholded based on the individual maximum connectivity value within a tract. The maximum connectivity value was obtained with fslstats and voxels which had values of more than 5% of

the maximum connectivity value were kept in the analysis (Bennett, Madden, Vaidya, Howard, & Howard, 2011). Furthermore, tracts were binarized and combined by masking the PCC with the anterior-tract (final-tract; see Figure 5).

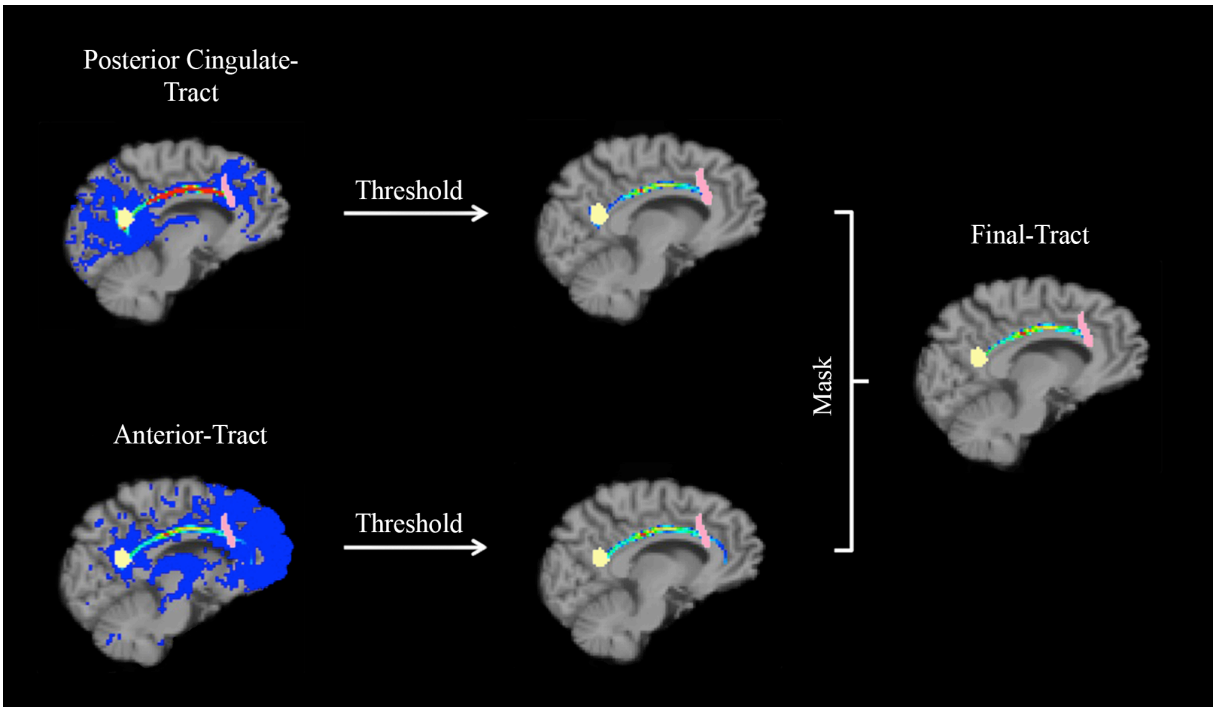

Figure 5. Steps to create the final cingulum tract. Heat colors in the cingulum tract represent higher probability. Threshold level is set on 5%. Yellow depicts the spherical ROI used for the posterior cingulate cortex, the pink color indicates the anterior ROI

Finally, we masked diffusion maps (FA/MD/AD/RD) with the binarized final-tract. We did not trace the entire cingulum bundle but just the posterior part. This procedure was applied to obtain more robust tract length and to ensure that only the cingulum bundle was traced. All tracts were visually inspected by SH. Subjects were excluded if tractography failed or a tract was touching the edge of the ROI (leading to 25 exclusions). In addition, participants were excluded if the transformation for the ROI into diffusion space failed (e.g., ROI depicted a hole). ROI transformation failed for 17 participants. The excluded participants did not differ in age, education, MMSE and gender (t-test, for all p>.07).

ANALYSIS OF RESTING-STATE FUNCTIONAL CONNECTIVITY

RS-FMRI DATA PREPROCESSING

The first 10 volumes of the time-series were discarded. Images were corrected for slice-timing using sinc interpolation to the median reference slice and realigned for head motion correction using the Statistical Parametric Mapping software (SPM8, Welcome Department of Imaging Neuroscience, Institute of Neurology, London, United Kingdom). Whole brain resting-state fMRI images were normalized to MNI space using a multi-step approach. First the averaged T1w image was co-registered to the mean resting-state fMRI echo planar image (EPI) using SPM8. The co-registered averaged T1w image was smoothed with a Gaussian kernel of 0.9 mm and normalized to MNI152 space using non-linear transformation with symmetric normalization (SyN) using Advanced Normalization Tools (ANTs; http://picsl.upenn.edu/software/ants). The resulting warp parameters were applied to the 4D EPI images, which were subsequently smoothed using FSL with a Gaussian kernel of 4 mm. Four participants were excluded because of excessive head motion (>3 mm, mean for included participants: 0.35 mm).

RS-FMRI CONNECTIVITY

The Data Processing Assistant for Resting-State fMRI (DPARSF) software package (Chao-Gan & Yu-Feng, 2010) and the Resting-State fMRI Data Analysis Toolkit (REST; http://www.restfmri.net) (X.-W. Song et al., 2011) were used for calculation of the functional connectivity maps. After normalization and pre-processing of the functional images the linear drift was removed using DPARSF's detrend. A temporal bandpass filter (0.01–0.08 Hz) was applied to reduce low-frequency drifts and physiological high-frequency noise. To generate functional connectivity maps, we created a 6mm spherical seed in the medial PCC cortex (MNI coordinate 0, -53, 26) based on (Van Dijk et al., 2010). Head motion realignment parameters (3 rotations and 3 translations) and signals from the white matter and CSF were

regressed out during the calculation of functional connectivity maps. For whole brain analysis white matter and CSF signals were extracted based on the mask provided by the REST toolkit. Pearson's correlation coefficient between the averaged time course at the seed ROI and each brain voxel's time course were computed. The correlation maps were converted to z-scores using Fisher's r-to-z transformation. The individual z-maps were then entered into a random effects analysis. In order to determine the peak correlation between the PCC ROI and the medial prefrontal cortex (mPFC) region, a one-sample t-test was performed on the z-maps that were created from the PCC ROI in a voxel-wise manner. Because of the relatively large number of subjects in our analysis, we chose a rather conservative statistical threshold, (p<0.01x10^{-8}, FWE corrected) for the initial voxel-wise connectivity maps. We then created a second 6mm spherical ROI in the mPFC (MNI coordinate 0, 62, -6) and subsequently reran the analysis. This time we concentrated our analysis on the correlation strengths between the PCC and mPFC seed ROIs. Again, the resulting Pearson correlation coefficient between two regions was converted to z values using Fisher's r-to-z transformation.

BEHAVIORAL ASSESSMENT

All participants completed an extensive cognitive and sensory-motor test battery.

COGNITIVE PERFORMANCE

The following cognitive outcome measures were assessed: a) processing speed, b) verbal fluency, c) memory and d) executive functions.

a) Processing speed (PS): PS was measured with the Digit Symbol-Coding Test of the Wechsler Adult Intelligence Scale (WAIS; Von Aster, Neubauer, & Horn, 2006). In this test, numbers from 1-9 are presented, each with a corresponding symbol. The aim is to fill in the blanks under additional rows of numbers by drawing the corresponding symbol below the number as fast as possible. The number of correct symbols drawn in 120 seconds was

recorded. The second PS measure was time to task completion of the Trail Making Test part A (TMT-A; Reitan & Wolfson, 1985).

b) Verbal fluency: Verbal fluency was assessed using the Regensburger word fluency test (Regensburger Wortflüssigkeits-Test (RWT); Aschenbrenner, Tucha, & Lange, 2000). Participants were asked to name as many animals as possible within two minutes.

c) Memory: Immediate and delayed episodic memory was measured using the German version of the Ray Auditory Verbal Learning Task (RAVLT; Rey 1964) (Verbaler Lern- und Merkfähigkeitstest (VLMT); Helmstaedter, Lendt, & Lux, 2001). In the immediate verbal recall phase, participants had to recall a list of 20 words immediately after an examiner presented the list verbally. This procedure was repeated 5 times. The score for immediate verbal recall was the sum of words recalled per session. Delayed verbal recall score was the number of words that participants remembered after an unexpected retrieval after a 20 minute break; Figural memory capacity was assessed using the DCS (*Diagnosticum für Cerebralschädigung* a diagnostic method for cerebral impairment). Participants were shown consecutively and without time constraints 9 figures printed on cards. Each figure consisted of 5 lines. Participants were instructed to look at the figures carefully and to remember them as accurately as possible. After the last card was shown, participants were encouraged to reconstruct all previously presented figures using 5 12cm long, wooden sticks. The test consisted of 6 runs and was either finished after 6 trials or when all 9 figures were reconstructed. All remaining runs were then scored as 9. The maximum score for the DCS was 54. There was no constraint concerning the order in which participants reproduced the figures.

d) Executive functions (EF): Two sub-components of executive functioning, inhibition and task-switching, were assessed. Inhibition was measured using a computerized version of the Stroop task (Vienna Test System, Schuhfried). In the Stroop task, participants are asked to

name the color in which the words are displayed as fast as possible. The inhibition score is the ratio between the median reaction time for congruent and incongruent stimuli. Task-switching was measured using the TMT. The task-switching score is the difference between time required to complete TMT part B (TMT-B) minus time required for TMT-A.

MOTOR BEHAVIOR

We obtained the following motor outcome measures a) manual dexterity, b) motor taping speed and c) grip force.

a) Manual dexterity was measured using the grooved pegboard (Lafayette Instrument Company, Lafayette, IN 47903 USA; model 32025). This test consists of a board with 25 holes, which have randomly aligned slots and pegs with a key along the side, which fit into the holes when rotated accordingly. Participants were asked to fill all of the holes with pegs as fast as possible. Pegs were placed from left to right with the right hand and from right to left with the left hand. Time was measured from the moment participants picked up the first peg until all the holes of the board were filled.

b) The amount of motor taps executed in 32 seconds was measured using the tapping test from the motor performance series (MLS; Vienna Test System, Schuhfried). Participants were asked to tap as many times as possible on a 4×4 cm metal plate with a pen-like device. Both hands were tested.

c) Grip force was measured using a hydraulic hand dynamometer (Model SH5001, Saehan Corporation, Korea). Participants were asked to sit upright, with the shoulder in a neutral position, elbow in 90° flexion, the forearm in a neutral position and with a 0°–30° wrist extension. Data was collected alternately for the right and left hand with a break of 30 seconds between measurements. Participants were asked to keep the force stable for 4 seconds for each trial. Three measurements per hand were collected. If the third measurement was the highest, data collection continued until performance dropped under a previous measurement.

Grip force score represents the mean of the three highest measurements for each participant in kilograms.

COVARIATES

Analyses were adjusted for several potential confounders, which were have been demonstrated to be associated with age, behavioral and brain outcome measures.

Blood pressure was obtained using an automated blood pressure cuff (Model M6, HEM-7211-E; Omron Corporation, Kyoto, Japan). Measurements were conducted three times at the same day (roughly 2.5-3 hours apart) and the average for the diastolic measurement was used for analysis (Beauchet et al., 2013; Marcus et al., 2011).

Education depict years spend until achievement of highest degree of education based on self-report.

A ratio between the sum of gray matter (GM) and white matter (WM) volume and the intracranial volume (ICV) was calculated as a measure of overall brain atrophy ((WM+GM Volume)/ICV Volume) (all scores obtained by FreeSurfer v5.3.0; http://surfer.nmr.mgh.harvard.edu).

STATISTICAL ANALYSES

All statistical analyses were performed using IBM SPSS Statistics for Mac OS X, Version 19.

To ensure that extreme cases did not drive associations, outliers of the dependent and independent variables (i.e., values three standard deviations above or below the mean) were removed.

For better comparisons between different cognitive and motor tests along with brain parameters all scores were standardized using z scores. In addition, behavioral scores where higher numbers represent worse performance were multiplied by -1.

First, to determine the associations between structural or functional connectivity with behavioral outcome measures we created a general linear model (GLM) that was adjusted for

age, gender, education, diastolic blood pressure and atrophy. Second, to test if the functional connectivity explains significant additional variance in our behavioral data on top of the variance explained by structural connectivity, we used hierarchical regression analysis. Separate regressions were conducted for each structural connectivity measure. All models included age, gender, education, diastolic blood pressure and atrophy as covariates of no interest. The level of significance for all tests was set to p=.05, uncorrected for multiple comparisons unless otherwise indicated.

Eta-squared (η^2) was calculated as effect size by dividing the Type III Sum of Squares of the factor of interest by the Total Sum of Squares ("Corrected Total" in SPSS). Preliminary analysis revealed that white matter integrity was significantly correlated between the left and right hemispheres; therefore, we further only analyzed the left cingulum tract and only motor behavioral scores from the dominant (right) hand.

5.2.3 RESULTS

Demographic characteristics of study participants and overview of all behavioral tasks and brain parameters can be found in Table 6. All behavioral measures and several structural connectivity measures (i.e., MD, AD and RD) showed associations with age.

Table 6. *Demographic Characteristics of the Study Participants*

Variable	N	M (SD)	r^{age}	p
Age (years)	165	70.15 (4.50)		
Men (N (%))	165	81 (49%)		
MMSE	165	28.85		
Education Years	165	14.53 (3.46)		
Blood Pressure diastolic (mmHg)	165	81.70 (9.85)		
Cognition:				
Processing Speed				
Digital Symbol Test	165	58.93 (12.03)	-.22	**.004**
TMT-A (s)	163	36.78 (10.83)	-.23	**.003**
Verbal Fluency				
Verbal Fluency	163	25.91 (5.79)	-.25	**.002**
Memory				
Immediate Recall	164	57.08 (8.71)	-.25	**.001**
Delayed Recall	164	12.10 (2.68)	-.23	**.003**
Visual Memory	163	32.00 (11.56)	-.30	**.001**
Executive Functions				
Task-Switching	160	51.08 (22.98)	-.24	**.002**
Inhibition	159	1.10 (.08)	-.17	**.008**
Motor Performance:				
Pegboard (s)	164	73.20 (11.97)	-.40	**<.001**
Tapping (number)	162	191.04 (20.85)	-.24	**.003**
Grip force (kg)	163	33.38 (10.66)	-.21	**.008**
Cingulum Measures				
Volume (ml)	164	1992.48 (437.77)	-.04	.635
FA	164	$4.7x10^{-1}$ ($3.6x10^{-2}$)	-.06	.484
MD	165	$7.6x10^{-4}$ ($3.0x10^{-5}$)	.32	**<.001**
AD	164	$1.2x10^{-3}$ ($4.5x10^{-5}$)	.27	**.001**
RD	165	$5.5x10^{-4}$ ($3.9x10^{-5}$)	.22	**.005**
rs-fMRI	165	$7.7x10^{-1}$ ($2.7x10^{-1}$)	-.08	.306

Abbreviations: AD=axial diffusivity FA=fractional anisotropy; kg=kilogram; M=mean; MD=mean diffusivity; ml=milliliter; mmHg=millimeter of mercury; MMSE=mini-mental state examination; RD=radial diffusivity; r^{age}=Pearson's correlation with age; rs-fMRI=resting-state functional connectivity; s=seconds; SD=standard deviation; TMT-A=trail making test part A

There was no significant relationship between structural and functional connectivity measures. In addition, the volume of the cingulum bundle was neither associated with the diffusion parameters nor functional connectivity (Table 7).

Table 7. *Correlations between Neuroimaging Parameters*

		rs-fMRI	Vol.	FA	MD	AD
rs-fMRI	r p					
Vol.	r p	-.031 .691				
FA	r p	-.004 .964	-.058 .465			
MD	r p	-.019 .810	-.009 .905	**-.490** <.001		
AD	r p	.026 .745	-.122 .122	**.470** <.001	**.486** <.001	
RD	r p	-.029 .709	.035 .654	**-.864** <.001	**.851** <.001	-.028 .719

Abbreviations: AD=axial diffusivity FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; rs-fMRI=resting-state functional connectivity; Vol.=cingulum bundle volume
Significance of associations do not change when adjusting for age, gender, education, diastolic blood pressure and atrophy

Out of all cognitive measures only verbal fluency was significantly associated with white matter integrity whereas functional connectivity was significantly associated with TMT-A and verbal fluency performance (Table 8). For motor behavior, we observed a significant association between structural connectivity measures (i.e., FA, MD and RD) and grip force. Furthermore, functional connectivity strength was positively associated with grooved pegboard performance (Table 9). However, after controlling for multiple comparisons none of the behavioral tests remained significantly associated with the connectivity measures.

Table 8. *Associations between Brain Connectivity Measures and Cognition*

				95% CI			
		N	**β**	**low**	**high**	**η^2**	**p**
Digital Symbol Test	FA	164	.026	-.121	.173	<.001	.723
	MD	165	.066	-.087	.220	.004	.395
	AD	164	.078	-.071	.228	.006	.303
	RD	165	.008	-.142	.158	<.001	.916
	rs-fMRI	165	.141	-.003	.284	.019	*.054*
Trail Making Test Part A	FA	162	.060	-.095	.215	.003	.443
	MD	163	-.078	-.239	.083	.005	.341
	AD	162	.042	-.118	.203	.002	.604
	RD	163	-.101	-.258	.056	.009	.207
	rs-fMRI	163	.198	.047	.349	.038	**.011**
Verbal Fluency	FA	162	.144	-.004	.293	.012	*.056*
	MD	163	-.011	-.168	.147	<.001	.892
	AD	162	.165	.013	.318	.025	**.034**
	RD	163	-.107	-.259	.046	.010	.169
	rs-fMRI	163	.146	.000	.291	.021	**.050**
Immediate Recall	FA	163	-.075	-.223	.073	.005	.317
	MD	164	.060	-.095	.215	.003	.445
	AD	163	.014	-.139	.167	<.001	.857
	RD	164	.064	-.087	.215	.004	.404
	rs-fMRI	164	.042	-.106	.191	.002	.574
Delayed Recall	FA	163	-.047	-.199	.106	.002	.546
	MD	164	.092	-.068	.251	.007	.257
	AD	163	.049	-.108	.207	.002	.538
	RD	164	.066	-.089	.221	.004	.403
	rs-fMRI	164	.041	-.112	.193	.002	.600
Visual Memory	FA	162	.010	-.135	.155	<.001	.895
	MD	163	-.029	-.184	.125	<.001	.707
	AD	162	.038	-.115	.190	.001	.628
	RD	163	-.047	-.197	.103	.002	.539
	rs-fMRI	163	-.013	-.160	.133	<.001	.857
Task-Switching	FA	159	.095	-.059	.250	.009	.223
	MD	160	-.120	-.279	.039	.013	.138
	AD	159	-.022	-.181	.136	<.001	.782
	RD	160	-.127	-.283	.029	.015	.109
	rs-fMRI	160	-.076	-.227	.075	.006	.321
Inhibition	FA	158	.093	-.066	.252	.008	.248
	MD	159	-.034	-.202	.134	.001	.689
	AD	158	.086	-.077	.248	.007	.299
	RD	159	-.098	-.262	.066	.009	.238
	rs-fMRI	159	.039	-.120	.199	.001	.625

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; rs-fMRI=resting-state functional connectivity

β values represent the increase in standard deviation (SD) in cognitive performance with 1 SD increase in connectivity measures

Adjusted for age, gender, education, diastolic blood pressure, atrophy

Table 9. *Associations between Brain Connectivity Measures and Motor Behavior*

				95% CI			
		N	β	low	high	η^2	p
Pegboard (dominant hand)	FA	163	.053	-.092	.197	.003	.474
	MD	164	.039	-.112	.190	.001	.611
	AD	163	.089	-.059	.237	.007	.239
	RD	164	-.019	-.167	.129	<.001	.800
	rs-fMRI	164	.233	.096	.371	.054	**.001**
Tapping (dominant hand)	FA	161	.117	-.030	.264	.013	.119
	MD	162	.015	-.144	.174	<.001	.853
	AD	161	.148	-.004	.299	.020	*.055*
	RD	162	-.081	-.233	.072	.006	.297
	rs-fMRI	162	.098	-.048	.234	.009	.186
Grip Force (dominant hand)	FA	162	.109	.020	.198	.011	**.017**
	MD	163	-.104	-.200	-.009	.009	**.032**
	AD	162	-.016	-.108	.075	<.001	.726
	RD	163	-.122	-.214	-.031	.014	**.009**
	rs-fMRI	163	-.062	-.152	.029	.003	.181

Abbreviations: AD=axial diffusivity; CI=confidence interval; FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; rs-fMRI=resting-state functional connectivity
β values represent the increase in standard deviation (SD) in motor performance with 1 SD increase in connectivity measures
Adjusted for age, gender, education, diastolic blood pressure, atrophy

Hierarchical regression analyses were assessed for behavioral tests, which showed at least a trend (p<.055, uncorrected for multiple comparisons) towards significance in the association with connectivity measurements when adjusted for age, gender, education, diastolic blood pressure and atrophy.

First, the structural connectivity measures were entered (FA, MD, AD or RD), followed in the second step by the functional connectivity measure. Table 10 demonstrates that adding functional connectivity to any model with structural connectivity (i.e., FA/MD/AD/RD) as predictor for TMT-A a significant additional proportion of the variance can be explained (i.e., ~4%). A significant increase in model fit was also observed for predicting DST performance with AD as predictor of structural connectivity and verbal fluency performance with RD as predictor of structural connectivity. The fit for the remaining models predicting DST and verbal fluency performance depicted a considerable trend towards significance when adding

functional connectivity measures in the second step. Table 11 presents the multiple hierarchical regression analyses for motor behavior. Model fit improved significantly for pegboard performance when entering functional connectivity. Functional connectivity did not explain any significant additional variance in the regression analysis of structural connectivity and grip force or tapping performance.

Table 10. *Hierarchical Regression Analysis for Cognition*

		Step I: structural connectivity					Step II: functional connectivity added						
		B	**SE**	**p_{pred}**	**F**	**R^2**	**B**	**SE**	**p_{pred}**	**F**	**ΔR^2**	**ΔF**	**p_{mod}**
Digital Symbol Test	FA rsfMRI	.026	.074	.723			.028 *.142*	.074 *.073*	.700 *.054*				
	Model				5.04	.161				4.93	.020	3.77	*.054*
	MD rsfMRI	.066	.078	.395			.063 *.140*	.077 *.073*	.412 *.057*				
	Model				5.23	.166				5.09	.019	3.68	*.057*
	AD rsfMRI	.078	.076	.303			.071 **.143**	.075 **.072**	.344 **.050**				
	Model				5.22	.166				5.12	.020	3.89	**.050**
	RD rsfMRI	.008	.076	.916			.008 *.141*	.075 *.073*	.918 *.055*				
	Model				5.09	.162				4.97	.019	3.73	*.055*
Trail Making Test Part A	FA rsfMRI	.060	.078	.643			.062 **.194**	.077 **.077**	.424 **.013**				
	Model				2.38	.084				3.02	.036	6.36	**.013**
	MD rsfMRI	-.078	.082	.341			-.082 **.200**	.080 **.077**	.305 **.010**				
	Model				2.29	.081				3.01	.039	6.81	**.010**
	AD rsfMRI	.042	.081	.604			.030 **.194**	.080 **.077**	.704 **.013**				
	Model				2.23	.079				2.88	.036	6.36	**.013**
	RD rsfMRI	-.101	.079	.207			-.100 **.198**	.078 **.076**	.202 **.011**				
	Model				2.42	.085				3.11	.038	6.71	**.011**
Verbal Fluency	FA rsfMRI	.144	.076	*.056*			.146 *.143*	.074 *.073*	.052 *.053*				
	Model				5.00	.162				4.09	.020	3.80	*.053*
	MD rsfMRI	-.011	.080	.892			-.013 *.146*	.079 *.074*	.868 *.051*				
	Model				4.13	.137				4.16	.021	3.88	*.051*
	AD rsfMRI	**.165**	**.077**	**.034**			**.159** *.139*	**.077** *.073*	**.040** *.060*				
	Model				4.90	.159				4.78	.019	3.6	*.060*
	RD rsfMRI	-.107	.077	.169			-.106 **.145**	.076 **.074**	.167 **.050**				
	Model				4.50	.148				4.49	.021	3.91	**.050**

Abbreviations: AD=axial diffusivity; FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; rsfMRI=resting-state functional connectivity; p_{prep} and p_{mod} represent the significant values for the predictor and the ΔR^2 respectively

ΔR^2 represents the change in R^2 when rsfMRI measure is added to the model after the diffusion parameter

All models include age, gender, education, diastolic blood pressure, atrophy as covariates of no interest. All models for step I were significant $p<.05$

Table 11. *Hierarchical Regression Analysis for Motor Behavior*

		Step I: structural connectivity					Step II: functional connectivity added						
		B	**SE**	**p_{pred}**	**F**	**R^2**	**B**	**SE**	**p_{pred}**	**F**	**ΔR^2**	**ΔF**	**p_{mod}**
Pegboard (dominant hand)	FA	.053	.073	.474			.056	.071	.436				
	rsfMRI						**.231**	**.070**	**.001**				
	Model				6.33	.196				7.31	.052	10.80	**.001**
	MD	.039	.077	.611			.034	.074	.644				
	rsfMRI						**.233**	**.070**	**.001**				
	Model				6.21	.192				7.25	.053	11.06	**.001**
	AD	.089	.075	.239			.077	.073	.291				
	rsfMRI						**.233**	**.070**	**.001**				
	Model				6.35	.196				7.39	.054	11.14	**.001**
	RD	-.019	.075	.800			-.019	.073	.795				
	rsfMRI						**.233**	**.070**	**.001**				
	Model				6.17	.191				7.22	.054	11.11	**.001**
Tapping (dominant hand)	FA	.117	.074	.119			.118	.074	.114				
	rsfMRI						.095	.073	.198				
	Model				5.32	.172				4.82	.009	1.67	.198
	MD	.015	.080	.853			.013	.080	.868				
	rsfMRI						.097	.074	.189				
	Model				4.73	.155				4.33	.009	1.74	.189
	AD	*.148*	*.077*	*.055*			*.143*	*.076*	*.063*				
	rsfMRI						.094	.073	.198				
	Model				5.34	.172				4.84	.009	1.67	.198
	RD	-.081	.077	.297			-.080	.077	.298				
	rsfMRI						.097	.073	.187				
	Model				4.94	.161				4.51	.009	1.76	.187
Grip Force (dominant hand)	FA	**.109**	**.045**	**.017**			**.108**	**.045**	**.017**				
	rsfMRI						-.063	.045	.166				
	Model				59.33	.697				51.43	.004	1.94	.166
	MD	**-.104**	**.048**	**.032**			**-.104**	**.048**	**.032**				
	rsfMRI						-.061	.045	.178				
	Model				58.91	.694				51.03	.004	1.83	.178
	AD	-.016	.046	.726			-.015	.046	.752				
	rsfMRI						-.057	.045	.208				
	Model				57.97	.692				50.11	.003	1.60	.208
	RD	**-.122**	**.046**	**.009**			**-.123**	**.046**	**.008**				
	rsfMRI						-.062	.045	.167				
	Model				60.16	.697				52.15	.004	1.93	.167

Abbreviations: AD=axial diffusivity; FA=fractional anisotropy; MD=mean diffusivity; RD=radial diffusivity; rsfMRI=resting-state functional connectivity; p_{prep} and p_{mod} represent the significant values for the predictor and the ΔR^2 respectively

ΔR^2 represents the change in R^2 when rsfMRI measure is added to the model after the diffusion parameter

All models include age, gender, education, diastolic blood pressure, atrophy as covariates of no interest. All models for step I were significant $p<.05$

5.2.4 DISCUSSION

Our study showed that white matter integrity within the cingulum bundle is associated with age, which corroborates previous findings. In general, white matter integrity throughout the entire brain is reported to decline with age (Bennett & Madden, 2014). Previous studies that investigated more specifically the relationship between white matter integrity of the cingulum bundle and age also observed an age-related decline. Principally, FA was persistently negatively associated with age whereas the relationship between diffusion metrics was not consistent across studies. Using the tractography approach, previous work showed that older participants differ significantly from young participants in the cingulum's FA and RD but not MD or AD (Davis et al., 2009; Zahr et al., 2009). Interestingly, in a tract-based spatial statistics study by Salami et al. (2012) the MD within the cingulum was not associated with age whereas a decrease in MD with age on the whole brain level was apparent. However, a recent study conducted by Borghesani et al. (2013) observed an age-related decline in white matter integrity for all diffusion metrics within the cingulum bundle. Unfortunately, large differences in sample characteristics between studies make it difficult to relate our results to previous findings. First, Salami and colleagues (2012) investigated white matter integrity over a large age range, including participants as young as 25 which clearly leads to larger variability within the data. Even though the age range was smaller in the study conducted by Borghesani et al. (2013) (age range=54-89), it spanned 35 years while our study is restricted to an age range of 21 years (age range=64-85).

In contrast to structural connectivity, we observed no relationship between functional connectivity and age. In a recent review, Dennis and Thompson (2014) concluded that DMN functional connectivity decreased with age. It is important to mention that most of the studies included in the review based their assumption on group comparisons between young and older participants (Andrews-Hanna et al., 2007; Damoiseaux et al., 2008; Wu et al., 2011).

However, in addition to a group comparison Andrews-Hanna and colleagues (2007) also investigated the relationship between age and functional connectivity within a group of older participants aged 60 to 90. They found a significant decrease in connectivity with increasing age. To gain a more clear-cut picture about the difference of functional connectivity strength over the life span Onoda and colleagues (2012) as well as Mevel and colleagues (2013) included a sample between 36 to 86 and 19 to 80 years of age respectively in their cross-sectional analyses. Results from both studies delineated a linear negative association between age and functional connectivity strength within the DMN. More precisely, Mevel et al. (2013) also reported a negative linear association of the PCC–mPFC functional connectivity strength and increasing age. To the best of our knowledge, Persson et al. (2014) were the first to systematically investigate longitudinal functional connectivity changes within the DMN in a relatively large sample of healthy aging participants. Within a test-retest period of 6 years the authors reported no relationship between age and functional connectivity change between the PCC and mPFC ROI.

According to the disconnection hypothesis deterioration in structural connectivity between linked brain regions could lead to a decrease in functional connectivity within the two connected areas (Bennett & Madden, 2014). This idea is supported by an earlier study of Andrew-Hanna and coauthors (2007). They reported an association between white matter integrity and functional connectivity strength between PCC and mPFC ROI in older participants. However, we did not observe an association between white matter integrity and functional connectivity in the cingulum bundle. This could be due to the absence of variation in functional connectivity strength with age in our sample of healthy older adults. In addition, this finding could be potentially explained by indirect functional connectivity pathways that could compensate for any loss of functional connectivity through the deteriorated white matter of the cingulum bundle. Previous longitudinal studies support this idea. While the age-

related decrease in structural connectivity seems established (Barrick et al., 2010), first longitudinal functional connectivity data depict stability over a 6 year time period (Persson et al., 2014).

One of the main goals of this study was to investigate if the combined information of structural and functional connectivity between brain areas connected through the cingulum tract could be a better predictor for cognitive and motor behavior outcome measures. We therefore investigated different cognitive domains and motor behaviors, which are consistently reported to be associated with age (Grady et al., 2010; Seidler et al., 2010). First, we examined the relationship between behavioral measures and structural connectivity. Structural connectivity was in previous studies reported to be associated with processing speed or executive functions (Fjell & Walhovd, 2010; Raz & Rodrigue, 2006). In contrast to our hypothesis we did not observe such a relation. However, we did observe an association between semantic verbal fluency and white matter integrity. This finding was in accordance with a former study by Metzler-Baddeley et al. (2012) who found a relationship between the anterior cingulum tract and semantic verbal fluency. In addition, grip strength was significantly related with structural connectivity. In general, grip strength is associated not only with physical but also mental health (e.g., depression) (Rantanen, Harris, et al., 2000; Rantanen, Penninx, et al., 2000; Syddall, Cooper, Martin, Briggs, & Aihie Sayer, 2003). It is reported to be clearly associated with age (Frederiksen et al., 2006) but underlying mechanisms of grip strength ability still need to be clarified. There is clear evidence that not only muscle mass/quality but also neural control affects motor performance in older adults (Seidler et al., 2010). In a functional MRI analysis Noble et al. (2011) found that with increased generated strength brain regions included motor cortical areas, the cingulate gyrus and medial frontal areas showed higher activation in older compared to younger participants. It could therefore be argued that grip strength decline is associated with neuroanatomical and

functional age-related alterations. It would be interesting to focus on tracts more specifically related to motor control (e.g., superior longitudinal fasciculus and corticospinal tract) to see if degeneration of these tracts is an even better predictor of grip strength. Discrepancies between our findings and results from former studies could be ascribed to the fact that we investigated a very homogenous sample of older highly educated participants, who did not show any signs of cognitive impairment or dementia, whereas other studies often include less cognitive healthy samples in which the association between cingulum bundle integrity and function might be more apparent due to the larger variability in these measures. In addition, the age range of our participants was relatively small, which could have led to less variance in the variables of interest compared to other studies.

Second, we analyzed the relationship between functional connectivity strength and behavioral measurements. We observed that performance on both cognitive and motor behavioral tasks were related to functional connectivity strength. Interestingly, of those behavioral measures associated with functional connectivity strength in our study, grooved pegboard performance and the digit-symbol coding task were previously reported to load on a "visuomotor speed and dexterity" factor when classifying behavioral outcome measures using a principal component analysis (Voineskos et al., 2012). In addition, we found that semantic verbal fluency was associated with functional connectivity strength. Because participants had to write down the answers and because processing speed is a major predictor of verbal fluency (Bryan, Luszcz, & Crawford, 1997; Salthouse, 2005) we suggest that verbal fluency in our study also contains a large visuomotor speed and dexterity component. In conclusion, our results show that maintaining higher synchronous intrinsic functional connectivity protects for age-related decrease in processing speed tasks or tasks with a high PS or dexterity component. This is of high interest since in PS ability is not only reported to be clearly associated with increasing age but also PS is one of the strongest predictors of cognitive performance in older

adults. Slowed PS is assumed to be the underlying mechanism of age-related decline in many higher-order cognitive functions, such as working memory and executive functions (Salthouse, 1996; Salthouse et al., 2003). Associations between PS and functional connectivity strength have been reported previously. Andrews-Hanna et al. (2007) found significant associations between PCC-mPFC connectivity strength and processing speed ability in older adults. A study with a sample with a comparable age-range as the one in our study also showed an association between cognition and connectivity strength (Damoiseaux et al., 2008). More specifically, it showed that processing speed and other cognitive measures such as attention, concentration, and executive functioning were related to connectivity strength in the anterior DMN, which comprised the superior frontal gyrus, posterior cingulate and bilateral middle temporal gyrus and superior parietal regions.

We explored if models that incorporated both structural as well as functional connectivity were better predictors of cognitive and motor behavior than models that only incorporated structural connectivity. Contrary to our hypothesis our results demonstrated that this was not the case. Although hierarchical regression analysis indicated an improvement of the model, no significant additive effect was found and the same results were found when analyzing the influence of structural and functional connectivity separately.

This study has some limitations. First, all findings are based on cross-sectional data and observed associations cannot be interpreted as causal. In addition, the associations found in this study were fairly small and did not survive a correction for multiple comparisons. However, we found brain-behavioral relations in a very healthy, highly functioning sample with a narrow age range even after controlling for several covariates such as age. Therefore, we believe that these observations contribute to our understanding of how brain structure and function and cognitive and motor performance are related in healthy aging.

This study stands out by applying an automatic procedure to analyze structural and functional connectivity measures of the cingulum tract in a large sample. Combining these multimodal findings with an extensive set of cognitive and motor behavioral outcome measures helps to gain specific insight into the neuroanatomical and physiological underpinnings of healthy aging. Further, by applying strict eligibility criteria the LHAB project aims to focus on the course of healthy aging.

In conclusion, we found no relationship between structural and functional connectivity of the cingulum bundle in a large well-educated sample of healthy older participants. In addition we found no association between functional connectivity strength and age. However, functional connectivity strength was a predictor for individual differences in cognitive performance, especially in tasks of visuomotor speed and dexterity. Based on the relevance of processing speed for age-related cognitive decline in general (Salthouse, 1996), it seems that maintained functional connectivity strength with age despite white matter integrity loss may be of great importance for healthy cognitive aging. Our data underline the value for combining multi-modal imaging and cognitive/motor performance measures in order to gain a better understanding of integrated brain functioning in healthy aging.

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RDS and LJ are faculty members of the LIFE Course: Evolutionary and Ontogenetic Dynamics.

6 GENERAL DISCUSSION

In the next section, findings of the current work are summarized and implications for future research are discussed. Some results in the existing literature were not replicated in the presented studies. One of the reasons for the discrepancies could be the specific features of the sample analyzed in this dissertation. Thus, in a second part, the concept of healthy aging and its impact on sample characteristics is discussed. Based on the findings of the two studies, future directions are elaborated. The general discussion closes with a short conclusion about the current work.

6.1 COMBINED WHITE MATTER STRUCTURAL MEASURES IN RELATION TO COGNITION IN HEALTHY AGING

In study 1 (*Relationship between cerebral macro- and microstructural white matter characteristics and executive functions in healthy older adults*) macro- and microstructural white matter characteristics were combined and related to two EF-subcomponents and PS performance, respectively. Based on previous studies, which found that white matter microstructural integrity is different within and outside WMH in general population (e.g., Vernooij et al., 2009), we hypothesized that white matter microstructural integrity would be lower within WMH than within the NAWM. Moreover, we hypothesized that cognitive performance would be positively associated with NAWM volume and white matter integrity within NAWM and WMH, but negatively with WMH volume. The analyzed data showed that within WMH, white matter integrity was generally lower compared to integrity within NAWM, confirming our hypothesis. Additionally, we found that only white matter integrity within NAWM, in contrast to white matter integrity within WMH, was associated with age.

These findings emphasize the importance of separating the two tissue types when analyzing white matter characteristics in the aging brain.

Combining white matter data with cognition we found that PS performance was positively related to NAWM volume and white matter integrity within NAWM. For the EF-subcomponents, results showed that inhibition performance was not associated with any white matter measures, while associations for task-switching were apparent but only for white matter integrity within WMH. Our results are in line with former DTI studies, which demonstrate that different EF-subcomponents are associated differently with white matter characteristics (Grieve et al., 2007; Jokinen et al., 2013; Kennedy & Raz, 2009; O'Sullivan et al., 2005). Therefore, discrepancies found between EF-subcomponents suggest that composite scores should be applied with caution, or even reconsidered in future studies, when investigating brain-behavior relationships in order to gain more specific results for the EF-subcomponents tested.

In conclusion, findings support the notion that intact white matter is important for cognitive functioning with increasing age and that the severity of the network disruption measured by grade of damage within WMH may be of higher relevance than WMH volume for cognitive performance.

We did not differentiate between periventricular and deep WMH, since our analyses focused on the difference between DTI measures within and outside NAWM in healthy older participants. However, distinction between those two categories of WMH may be of great interest since differences in development for periventricular and deep WMH are reported (Silbert et al., 2008; 2009). An additional separation of WMH based on brain lobes could be of significance, especially since the prefrontal-executive theory postulates that age-related deterioration of the frontal lobe is associated with performance in EF (West, 1996). Therefore,

studies might extend this investigation with information about the specific location of WMH to attain further insight into brain-behavior relationships.

6.2 Combined Brain Connectivity Measures in Relation to Behavioral Data in Healthy Aging

Study 2 (*Structural and functional connectivity in healthy aging: associations for cognition and motor behavior*) investigated the combined analyses of structural and functional connectivity of two brain regions in relationship with cognitive and motor performance. We hypothesized that an association between structural and functional connectivity is apparent. Additionally, we expected that structural and functional data together could account for more variance in cognitive and motor performance than each measurement alone. Data revealed that age was associated with structural connectivity but not functional connectivity. Contrary to our hypothesis and findings from previous studies (Andrews-Hanna et al., 2007), no relationship between structural and functional connectivity was apparent. Furthermore, our results showed that there was no additive effect by combining data from structural and functional connectivity, when investigating the association between behavioral performance and connectivity measures of the cingulum bundle. Though, for each connectivity measure, separate associations were apparent. Whereas structural connectivity was associated with grip force, functional connectivity strength was a predictor for individual differences in behavioral performance, especially in tasks of visuomotor speed and dexterity. Given the importance of processing speed within aging research, this finding is of substantial interest. In conclusion, it seems that maintenance of functional connectivity strength, despite loss of underlying microstructural integrity, is of importance for successful healthy aging and may be accomplished by compensatory mechanisms.

The idea about functional compensation for structural changes is not new and evidence is

found in task-based fMRI studies (e.g., Cabeza, Anderson, Locantore, & McIntosh, 2002). It may be also possible that white matter degeneration of the cingulum bundle has to drop under a certain threshold before decline in functional connectivity strength is apparent.

However, to verify that the functional connectivity strength could be maintained due to compensatory mechanisms over non-direct pathways, future studies might expand this work by analyzing additional white matter tracts. Furthermore, this study only investigated one specific tract within the DMN. Since connectivity strength within the DMN is commonly reported to be associated with major cognitive abilities such as memory performance (e.g., He, Carmichael, et al., 2012), gaining more insight into the relation between structural and functional connectivity seems to be of considerable interest in aging research.

6.3 CHARACTERISTICS OF SAMPLES IN AGING RESEARCH

The primary aim of this dissertation was to investigate the brain-behavior relationship in healthy aging participants. Next to new insights in how brain measures are related to behavior performance, some previous results could not be replicated with our dataset. Moreover, associations between neural and behavioral parameters found in our studies depicted rather small effect sizes and did not survive a correction for multiple comparisons. We think this discrepancy can be due to several reasons, which are mainly caused by an overarching problem: the absence of a clear definition for healthy aging. To date, a consensual characterization is missing and terms like active aging (WHO, 2002) or successful aging (e.g., Baltes & Baltes, 1990; Bowling & Dieppe, 2005; Rowe & Kahn, 1997) are used synonymously. Terminologies and definitions may roughly be categorized into approaches reflecting psychosocial or biomedical components or combination of those (Bowling & Dieppe, 2005). While biomedical theories focus more on mental and/or physical deterioration (Rowe & Kahn, 1997), psychosocial approaches emphasize the importance of life-satisfaction and view healthy aging as a dynamic process (Havighurst, 1963). Despite numerous

interpretations, healthy aging is mostly seen as a multidimensional construct and not just the absence of disease. However, a consensus about which specific components comprise such a multidimensional design is still missing. Additional difficulties arise since the term "healthy aging" is used in literature as a process and as an outcome measure. Thus, a first step towards a definition of healthy aging is a clearer answer to the question of what the relevant and interesting measurements are and how to obtain them. Moreover, the change of focus of healthy aging research, away from solely describing age-related functional decline, towards the examination of how cognitive functioning can be maintained and stabilized, is of great importance for the near future. Additionally, it is essential that the construct *healthy aging* has to be relevant for the community. This is crucial because discrepancies between elderly adults' subjective perceptions and their scores on objective measures can occur. To illustrate, a study by von Faber and colleagues (2001) demonstrated that subjective evaluations differ from quantitative measures, since significantly more participants saw themselves as successfully aged, than what was found in the quantitative results. Therefore, participative research should be promoted to include the perspective from older adults.

In order to achieve the goal of a distinct definition of a healthy aging concept, the biomedical and psychosocial models should be combined to enable a broader view of the construct healthy aging. Within an interdisciplinary team, perspectives from different academic disciplines and opinions from laypersons, such as elderly people, should be incorporated to find a consensual concept relevant to researchers, clinicians, and older adults. Moreover, what should be used as screening measures for a sample (e.g., what inclusion and exclusion criteria a person should meet) and what predictors should be investigated, needs to be stated more precisely.

We suggest that, with a clearer view about sample characteristics in healthy aging (e.g., age-range and cognitive status), future research may be able to reduce the likelihood of finding

results that are only applicable in one study but not in the other. To illustrate, different cutoff scores (as low as 24) for the MMSE are used for exclusion criteria throughout studies of healthy aging. Additionally, there is no clear-cut point from which participants are "classified" as older. Hence, studies can vary extremely in age-ranges (e.g., ranging from ~55 years to 85 years, including also middle aged participants). In comparison, the findings presented in this dissertation are based on measurements of the first time point of the LHAB database project. The project is characterized by strict exclusion criteria (e.g., MMSE>26) to prohibit participants with risk of mild cognitive impairment (MCI). Additionally, included participants had to be over 64 years of age resulting in a small age-range (ranging from age ~65 years to – 85 years) of the investigated sample. Furthermore, the sample was recruited from the close Zurich area and can be described as well-educated. Therefore, we believe that the absence of brain-behavioral associations, found in previous studies, could be explained by lower variability in our data. We base our assumption on findings, which indicate that inter-individual variability within cognitive performance (e.g., processing speed, memory, executive functions) increases with age among older participants (Christensen, 2001) or when comparing younger with older subjects (Hultsch, MacDonald, & Dixon, 2002; Sylvain-Roy & Belleville, 2014). In general, we could argue that we diminished variability within our data by analyzing a small age-ranged healthy group of elderly people.

Besides the absence of a clear definition of healthy aging, which could lead to differences in sample characteristics, the diversity in sample size and applied tests could further contribute to differences in brain-behavior associations. In studies investigating associations between brain measures and behavior performance, sample size can vary substantially, which could lead to differences in statistical power (reported sample sizes range from N~50 to N~900) (Kennedy & Raz, 2009; Vernooij et al., 2009). Additionally, rather small samples of younger versus older participants are compared. To illustrate, most studies included in a recent review

on functional brain connectivity in aging based their assumption on group comparisons between young and older participants (Dennis & Thompson, 2014). Comparing extreme groups could lead to an overestimation of age-related differences. Further, cohort effects, which are likely to be a problem in cross-sectional studies, may confound results.

Moreover, applied tests to describe a cognitive construct can differ between studies, which could lead to different associations. To illustrate, composite scores for certain cognitive domains are widely used when analyzing brain-behavior relationships (e.g., Andrews-Hanna et al., 2007; Vernooij et al., 2009). In contrast, we evaluated tests separately, especially for EF scores. Analyzing tests separately seems to be appropriate because of the substantial inconsistencies in the definition and conceptualization of EF and its subcomponents (Miyake et al., 2000).

In conclusion, by applying strict inclusion and exclusion criteria, the LHAB database project contributes to the evaluation of healthy aging. We hypothesize, and anticipate identifying, single or a combination of different predictors (e.g., leisure time activity, nutrition), which may be the cause for healthy aging trajectories (e.g., stability over time in a measured component like cognition or physical functioning).

6.4 FUTURE DIRECTIONS

We expected that our understanding about the brain-behavior relationship in healthy aging would be deepened by use of multimodal imaging. Within both studies, we found results that otherwise would not have been detected with separate measures for each modality. To illustrate, microstructural differences within WMH could be quantified, which would not be possible with a single modality approach. Our findings therefore support the view that multimodal imaging should be pushed in future work. As mentioned in the introduction, this thesis focused on the combination of MR images. Multimodal imaging is not restricted to the combination of multiple MRI sequences in that it also refers to the combination of different

neuroimaging techniques. For example, the combined recording for resting-state fMRI and electroencephalogram (EEG) data can help to optimize the evaluation of the dynamics of brain network. Whereas fMRI is known for its high spatial accuracy, EEG stands out for its high temporal resolution. Combining both modalities counterbalances the weakness of each modality and facilitates the deeper knowledge about the dynamics of the brain. However, despite the strong potential of multimodal imaging, joint analyses have to be used with caution. Specifically, processing pipelines are not as elaborate yet because technical and methodological difficulties still arise when fusing heterogeneous signals. To illustrate, information from different MR images can only be integrated when the acquired data is within the same "space". Since the space in which MR images are recorded can differ between MRI sequences, transformations of the images are required (Hodneland, Ystad, Haász, Munthe-Kaas, & Lundervold, 2012). Such an intra-subject registration of several MRI sequences is still challenging because images can differ substantially in their resolution (e.g., high-resolution anatomical vs. low-resolution diffusion images), which can result in misregistration. Moreover, ready to use pipelines for multimodal imaging are still unavailable; thus, multimodal analyses are mostly created in house, which leads to difficulties in understanding, and making comparisons between results from different studies. Further, some multimodal approaches still need manual adjustments, which makes the evaluation of big data sets nearly impossible (Khalsa et al., 2013). Moreover, recording multiple MR sequences is costly and time-consuming and could lead to a trade-off between time and scan quality. For example, when collecting several MR images, the scan duration might be problematic because participants cannot lie in a scanner for prolonged time. This seems like a minor issue but needs to be considered especially in aging research, where increased head motion artifacts are anticipated (Mowinckel, Espeseth, & Westlye, 2012). Additional increase in head movement is expected with longer scan duration, which affects the quality of the

collected imaging data. This problem can partly be solved with higher field strength magnets, since they are able to collect data with the same quality (e.g., signal to noise ratio, resolution) faster. With the increasing interest in multimodal analyses and the expanded interdisciplinary work between psychologists and computer scientists, there is no doubt that many of these shortcomings will be resolved in the near future.

Despite new findings in the field of brain-behavior relationships in healthy aging, results from both studies in this thesis are based on cross-sectional data. This is a limitation because no conclusions about causality can be drawn. However, both studies evaluated data from the LHAB database project, which is an ongoing longitudinal study with approximately four one-year follow-ups. Therefore, the studies presented in this thesis can be replicated in a longitudinal fashion in due time. The longitudinal data will be beneficial, in that several recent findings argue that cross-sectional neuroimaging results may differentiate substantially from longitudinal data. To illustrate, Barrick and colleagues (2010) found that age-related tract-based spatial statistic (TBSS) white matter changes, based on longitudinal data, are greater than those obtained from cross-sectional analyses. Raz et al. (2005) found similar results in their investigating of regional brain changes of specific ROIs. Their analyses showed that the rate of change exceeded the expected shrinkage anticipated from cross-sectional studies. Interestingly, studies analyzing functional connectivity data within the default mode network found contrasting results. Whereas most cross-sectional studies showed linear decline with age (Mevel et al., 2013; Onoda et al., 2012), a recent longitudinal study found no change in functional connectivity strength over a 6 year time span (Persson et al., 2014). The distinct prediction for structural and functional changes by cross-sectional and longitudinal studies depicts only one reason why longitudinal research designs should be emphasized. Additionally, longitudinal studies are preferential over cross-sectional studies since they can describe inter-individual and intra-individual changes. Moreover, changes

found in different variables over time can be related to each other. To illustrate, with the use of bivariate latent change scores (i.e., one specific but certainly not exclusive statistical approach to evaluated longitudinal data), studies examined lead-lag relationships for physical activity and cognitive decline (Ghisletta, Bickel, & Lövdén, 2006), or social engagement and processing speed (Lövdén, Ghisletta, & Lindenberger, 2005). With such analyses, the question about causality can be answered as the sequence in changes of different variables can be evaluated.

Taking this approach one step further, linking behavior data with multimodal imaging within a longitudinally study design would provide new and important insights into the brain-behavior relationship in the coming years. To illustrate, longitudinal analyses of the second study, which investigated structural and functional connectivity measures associated with behavioral performance, could not only reveal if decline in structural connectivity indeed leads to loss of functional connectivity, but also if and when structural and functional connectivity alterations could cause behavioral changes.

For such longitudinal study designs, one crucial and initial point, which has to be met, is high reliability of longitudinal MRI measurements. The understanding of the reliability is central for correct interpretation of changes found over time. In addition, statistical power to detect intra-individual change in longitudinal designs is highly associated with the reliability of the measurement. Findings from our own laboratory indicated that longitudinally analyzed DTI and gray matter parameters such as cortical thickness and surface areas have relatively high reliability (Liem, Hirsiger, et al., 2014; Madhyastha, Hirsiger, et al., 2014). However, reliability varies between measures (e.g., FA vs. AD for DTI, or cortical thickness vs. surface area for gray matter), and depends on applied processing steps, such as data smoothing. In general, often used neuroimaging processing software offers reliable measures, and longitudinal analyses seem to not be confounded by low test-retest reliability when applying

those tools; caution is recommended when choosing the appropriate settings for optimal longitudinal analyses, since small choices in the processing pipeline might have significant effects on the results.

Moreover, there are additional challenges, which have to be overcome in future longitudinal MRI studies. First, despite several software products, which have already implemented longitudinal models for more than two time points (e.g., VBM8-toolbox; http://dbm.neuro.uni-jena.de/vbm.html or FreeSurfer; http://surfer.nmr.mgh.harvard.edu), such a feature is still missing for certain analysis tools (e.g., tract-based spatial statistics (TBSS); Smith et al., 2006). With two time points, only a linear change can be evaluated. In contrast, the analysis of multiple time points enable a more sophisticated assessment since a clearer analysis of the course in change can be examined. This would also be of strong benefit to gain more insight in the process of the aging brain. It is still worth mentioning that TBSS analyses with more than two time points are possible. However, performing the analyses in a longitudinal fashion, rather than combining multiple cross-sectional analyses, requires strong programming skills and technical knowledge. Moreover, for resting-state fMRI analyses, no longitudinal pipeline exists to date. Therefore, efforts should be undertaken to create more ready-to-use pipelines, preferably by the software developer, which has implemented a model for longitudinal analyses of more than two time points since, a) certain pipelines are difficult to apply for users without elaborate programming skills (e.g., physicians, psychologists) and b) evaluation of several measurement points in time enables researchers to gain additional knowledge about the change trajectories of brain parameters. Moreover, MR image processing pipelines in the future should preferably be fully-automated to handle big data sets since a) sample sizes increased tremendously for MR studies over the last decade, and b) the boost in data sharing gives access to big data sets, which might not be analyzed when manual adjustments are needed for processing steps. Moreover, pipelines should also offer the

possibility to handle multimodal data. Since joint analyses of MR images have already gained in popularity in the recent years (especially the combination of resting-state and DTI sequences), the assumption that future pipelines will incorporate multimodal analyses is promising. It is perspicuous that such sophisticated pipelines cannot be created without deep knowledge in computer science. The need for new and more elaborate research tools clearly emphasizes the importance for interdisciplinary teams to work together. By cooperation with different branches like computer science and physics, there is no doubt that in the near future the described difficulties will be overcome, and ready-to-use tools for longitudinal multimodal analyses will be developed.

6.5 CONCLUDING REMARKS

Both empirical studies presented in this thesis found results, by utilization of multimodal imaging. These results would not be apparent if each modality was analyzed separately. Thus, our findings suggest that future studies apply a multimodal approach to complement the present findings based on one modality. Furthermore, both studies were conducted in the context of *healthy aging*; however, no consensual definition of "healthy aging" exists today, which complicates the comparison between results from different studies. A clear rational for healthy aging is therefore essential, and the development of such a definition has to be a primary aim for this field of research. With this work we make a significant contribution to the aging research by offering new insight into brain-behavior relationships and by highlighting challenges to be overcome in the research on facilitating healthy aging.

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8 CURRICULUM VITAE

PERSONAL DETAILS

Name:	Sarah Hirsiger
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EDUCATION

09/2011 – 09/2014	Fellow of the International Max Planck Research School *"The Life Course: Evolutionary and Ontogenetic Dynamics" (LIFE)* University of Zurich
10/2010 – 09/2014	PhD Student at the International Normal Aging and Plasticity Imaging Center (INAPIC), University of Zurich
10/2008 – 09/2010	Master of Science ETH with distinction in Human Movement Sciences and Sport with focus on Motor Control and Learning
10/2005 – 09/2008	Bachelor of Science ETH in Human Movement Sciences

RESEARCH GRANTS

10/2013 – 03/2014	SNF Doc.Mobility Fellowship Grant
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AWARDS

05/2014	Poster award (1st prize) of the Lizentianden, Masterstudierenden und Doktorierenden-Kongress (LiMaDoKo) in the category PhD Students
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PUBLICATIONS

Hirsiger, S., Mérillat, S., Erdin, C., Koppelmans, V., Narkhede, A., Brickman, A., & Jäncke, L. Relationship between cerebral macro- and microstructural white matter characteristics and executive functions in healthy older adults. *Manuscript submitted for publication*

Hirsiger, S., Koppelmans, V., Mérillat, S., Liem, F., Erdeniz, B., Seidler, R. D., & Jäncke, L. Different associations between cognition and motor behavior and cingulum bundle's structural and functional connectivity in healthy aging. *Manuscript submitted for publication*

Koppelmans, V., **Hirsiger, S.,** Mérillat, S., Jäncke, L., & Seidler, R. D. Cerebellar gray and white matter volume and their relation with age and motor function in healthy older adults. *Manuscript submitted for publication*

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Seidler, R. D., Erdeniz, B., Koppelmans, V., **Hirsiger, S.,** Mérillat, S., & Jäncke, L. Associations Between Age, Motor Function, and Resting State Sensorimotor Network Connectivity in Healthy Older Adults. *Manuscript accepted for publication*

Mérillat, S., Steiger, B., **Hirsiger, S.,** & Jäncke, L. Neuronal, behavioral and demographic predictors of performance in tasks of verbal fluency in healthy aging. *Manuscript in preparation*

Liem, F., Mérillat, S., Bezzola, L., **Hirsiger, S.**, Michel, P., Madhyastha, T., & Jäncke, L. Reliability and statistical power analysis of cortical and subcortical FreeSurfer metrics in a large sample of healthy elderly. *Manuscript submitted for publication*

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